



THE JOHNS HOPKINS PROSTATE LIBRARY

# ADVANCED PROSTATE CANCER TREATMENTS

Know Your Options When Your  
Cancer Comes Back

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M E D I C I N E



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### INTRODUCTION

JACEK L. MOSTWIN, M.D., D.PHIL. (OXON)  
*Professor of Urology*

Prostate cancer is the most common cancer in men and the third leading cause of death due to cancer in men. The work to find a cure for prostate cancer is worldwide and ongoing, and death rates for prostate cancer have been steadily declining, thanks to early detection and improved therapies. But too many men are still notified every day that their cancer has recurred. They are told that they have advanced cancer, and that they must now, with the counsel of their doctors, decide what to do about it.

Receiving the news that prostate cancer has recurred, often after years of undetectable or steady PSA results, is shocking and bewildering to most men, and often more devastating than their original cancer diagnosis. Many men react with fear when given the news, others with anger, and some with a sense of utter hopelessness. When prostate cancer recurs, it immediately raises numerous concerns and important questions. Is life all downhill from here? How will the cancer impact my future? Is cure still a possibility? What is the best therapy? How do I make the final treatment choice? Should I consider joining a clinical trial? How can I regain control of my life?

For more than a decade, the *Johns Hopkins Prostate Bulletin* has kept its readers abreast of the latest therapeutic strategies and approaches for men with newly diagnosed and advanced prostate cancer. As medical editor of the *Bulletin*, I am proud to play a role in helping them understand what to expect throughout the course of their disease and how to optimize the outcomes of therapy. By learning as much as you can about this disease, the therapies that are available to combat it, and the research into new treatments that is underway, fear and frustration can give way to hope and energy for life.

This special report, *Advanced Prostate Cancer Treatments*, features discussions with leading experts at Johns Hopkins on specific options for treating advanced prostate cancer—with the aim of helping you through this difficult process. Although there is currently no cure for advanced prostate cancer, there are ways to help control the spread of cancer and manage its symptoms without diminishing the quality of life.

In preparing *Advanced Prostate Cancer Treatments*, my goal has been to offer as much information as possible about recurrent prostate cancer and the available therapies used to treat it so



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you can work with your doctor(s) to select a treatment that is right for you. The contributors have highlighted the key issues you will be facing—and what to consider at each step of the way. Their advice is based on their experience in treating and educating men with advanced disease. I encourage you to discuss any of their insights and recommendations with your own doctors.

Even though a diagnosis of advanced cancer can be depressing, there is certainly good news to report. In the past few years, important research efforts have been made, with major work aimed at trying to understand the types of biological changes that occur as prostate cancer progresses. I am happy to report that these efforts are starting to pay off. We now have new classes of innovative, cancer-fighting drugs and treatments specifically targeted at various stages of the disease.

Treating recurrent prostate typically requires combinations of drugs and other therapies. As you will see, there are a variety of treatment options, including hormonal therapy, chemotherapy, and radiation therapy. There are also preventive steps that are now taken to offset bone loss that often comes with therapy.

Recurrent prostate cancer poses many new challenges for men and their treatment team. However, there are also ongoing clinical studies testing promising new “targeted” drugs that zero in on the cancer cells and bypass healthy tissue. You may want to consider joining one of these trials as a focus of your treatment.

This report also provides vital information about preserving skeletal mass, optimizing pain relief, and dealing with the depression that sometimes accompanies the cancer return. The value of maintaining hope in the face of a serious disease is covered in an interview with author-physician Jerome Groopman—and the final section of the report explores the relationship between treatment decisions and end-of-life decisions.

It is my hope that you will use *Advanced Prostate Cancer Treatments* to help plan an effective treatment strategy that works best for you. Although you may not have total control over your cancer, the key is to stay focused on your unique circumstances and work with members of your medical support team to find the treatment path that is best for you.

On behalf of the contributors, who have dedicated their lives to prostate cancer research and treatment, I extend my best wishes for your good health.

Jacek L. Mostwin, M.D., D.Phil. (Oxon)



## WHEN PROSTATE CANCER RECURS

**H. BALLENTINE CARTER, M.D.**, is professor of Urology, Oncology, and Director of the Division of Adult Urology at the Brady Urological Institute at Johns Hopkins. He is the primary author or co-author of more than six dozen major urological studies published in peer-reviewed journals, as well as the principal author or co-author of more than two dozen textbook articles on urology.

**E**ven though most men have the greatest respect for the skill of their surgeon or radiation oncologist, in the back of every survivor's mind is the worrisome thought that all of the cancerous cells have not been removed or obliterated and that the cancer is going to come back one day.

Most men have a high level of trepidation prior to each regularly scheduled PSA test. There's the unspoken uneasiness that a disease that was thought to be cured will reappear after a few years, and unleash all those bottled up feelings of sadness, fear, anger, and thoughts of impending death.

I've noted increased concern in this area over the past year, with many men contacting me for information about available treatment strategies for recurrent prostate cancer. The good news is that in the ongoing war against prostate cancer, progress is being made and cancer recurrence rates are plummeting. Twenty years ago, it used to be that many of the men diagnosed with prostate cancer clearly had tumors that had extended beyond the prostate, leaving them vulnerable to the recurrence of cancer, no matter what treatment they underwent. Thanks to the PSA test and digital rectal exam (DRE), however, men are now being diagnosed much earlier, when the cancer is still within the prostate, and they can be cured with local treatments directed at the prostate.

About 20 to 30% of men experience a detectable PSA level within ten years of surgery. These recurrence figures are getting better, and will continue to do so as more men have their cancer detected early. But what about the men who do experience a rise in their PSAs after the prostate was removed or irradiated? According to Dr. Patrick C. Walsh, former Urologist-in-Chief at the James Buchanan Brady Urological Institute, many men who fall into this category may not need to do anything for years.

This may come as a surprise to many prostate cancer survivors who think that the best course of action for recurrent cancer is action of some sort. But according to Dr. Walsh, the only men who need to do something right away are those who:

- have cancer that has spread to the bones
- are symptomatic from disease spread
- have a prostate cancer that is obstructing the kidneys or bladder



In such cases, hormonal therapy should be started immediately to slow the progression of the cancer. Regular treatments with drugs called LHRH agonists (medical castration) that reduce the production of testosterone, the fuel that stimulates tumor growth, will cause tumor regression, as will surgical removal of the testicles (surgical castration, or orchiectomy).

Hormonal therapy—also called hormonal or androgen ablation—is effective at turning off the body’s supply of male hormones, which prostate cells need to grow and develop. When the supply is shut off by drugs (i.e., LHRH agonists) or by removing the testicles, tumors generally shrink or regress. In the absence of testosterone, the prostate cancer may remain in remission for years.

Unfortunately, blocking the hormones is not the lethal blow we’d all like it to be because prostate cancer is heterogeneous—made up of prostate cancer cells with differing abilities to resist androgen withdrawal. This means that the cancer is actually a melting pot of a variety of cells. When the prostate cancer is confined to the gland and then is surgically removed or effectively irradiated, we hope that all cells are killed. But if some of these cancerous cells happen to escape to distant sites, their inherent diversity becomes a major challenge.

Certain cells are resistant to a hormone treatment that targets only one kind of cell and these resistant cells can grow and thrive in the absence of male hormones. These are called androgen-independent or androgen-insensitive cells. Prostate cancer that seems to defy hormonal therapy altogether is called hormone refractory disease. How prostate cancer cells become hormone refractory is an intense area of research. Identification of the mechanism these resistant cells use to continue growing could provide a new treatment for blocking growth.

What should you do if your PSA begins to rise? If there is no sign that cancer has spread except a rising PSA, no evidence has shown that starting hormonal therapy—the mainstay for 50 years in slowing prostate cancer—will prolong your life, and so there may be no advantage to beginning this therapy immediately.

The Veterans’ Administration Cooperative Urological Research Group study of 954 men with advanced prostate cancer who were randomized to immediate orchiectomy (removal of the testicles) or delayed hormonal therapy failed to show any difference in survival between men who underwent orchiectomy early versus those who started hormonal therapy when the cancer progressed. That’s because the cells that prove fatal are the hormone-insensitive cells. Hormone treatment has no effect on these cells, whether the therapy is started early or late.

When the bone scan is negative, Hopkins experts believe that there is no proven advantage to starting a therapy that has such negative effects on quality of life. Long-term side effects of androgen withdrawal include decreases in mental acuity, loss of bone (osteopenia and osteoporosis) and muscle mass (sarcopenia), decreased energy, loss of sexual function, and depression.



If a man's cancer has recurred—as determined by increased PSA—but has not metastasized to the extent that it is evident by other tests (bone scan) or symptomatic (e.g., bone pain), he can instead adopt a wait-and-see strategy. This entails being monitored closely by a physician so that hormonal therapy can be started when the cancer does progress and become evident.

**Every six months the physician should:**

1. Question the patient about signs and symptoms that could be the result of disease spread.
2. Perform a physical examination to check for any increase in the size of the tumor.
3. Check the PSA to track disease progression.
4. Perform a serum creatinine test to make sure kidney function is not being impaired.

**Every six to twelve months the physician should:**

1. Order a bone scan to find out if the cancer has spread to the bone.

Here's what happens when you start hormonal therapy or have an orchiectomy. The early results are generally so encouraging that many men mistakenly think that the cancer has been defeated. The tumor shrinks, PSA levels drop in the blood, and the patient feels better. But remember that only the hormone-dependent cancer cells have been affected, while the hormone-independent cancer cells continue to grow. Many patients believe that if their PSA falls to the undetectable range that the cancer has been cured. Unfortunately, this is not true. PSA falls because production of PSA is under the control of hormones. Cancer cells can stop making PSA but continue to grow.

How long does LHRH therapy or an orchiectomy keep the cancer at bay? The time frame varies from man to man. When androgen deprivation is started at the time a bone scan is positive, 25% of patients are alive five years after starting therapy; 10% survive a decade or more. Over time, however, the deadliest cancer cells eventually survive and progress because they are impervious to all currently available therapies.

As hormones begin to lose their effect on the tumor and PSA begins to rise yet again, some men will choose to enroll in a clinical trial aimed at killing cancer cells that standard therapy (androgen withdrawal) can't touch. As a trial participant, men may receive the latest medication or cutting-edge therapy provided by top specialists at leading healthcare facilities. If you're a terminally ill patient, clinical trials may also offer a real source of hope. And by contributing to the discovery of effective new treatments, participants may help others lead longer, healthier lives.



## Should You Join A Clinical Trial?

While there is a 15-year survival rate, on average, for a man whose prostate cancer has recurred after local therapy— which is good in the world of cancer—it is not good enough for the patient with advanced cancer.

Even though all patients want therapies that will keep their cancer in check, it is estimated that only 3% of the possible number of people who would be candidates for clinical trials of novel cancer agents actually enroll in the trials. We can't assume that we now have all the answers just because we at last have a life-extending drug like Taxotere. What will help push the science forward at a greater pace is having more men enroll in clinical trials of experimental prostate cancer therapies.

You might want to join a clinical trial for a number of reasons. If you have advanced prostate cancer, you might hope for remission, or even for a cure. You might see participation as providing access to free, high-quality treatment. You might be altruistic and simply want to help advance medical knowledge. Clinical trials also provide answers to more basic questions: Can an injection get the medicine to you faster than a pill? Does the newest painkiller make you less drowsy than the others? The engine of medical progress depends on data from clinical trials for fuel, but getting the best data requires the willing participation of hundreds or thousands of people—no doubt you've seen the recruitment ads that pepper newspapers and magazines.

Before you join a clinical trial, however, it's important to understand what's involved.

### The Structure of Clinical Trials

Studies always begin in test tubes and in animals. If results are promising, patient recruitment begins.

- **Phase I** evaluates drug safety in a few dozen subjects with advanced disease, determines dosage, and identifies side effects.
- **Phase II** involves up to a few hundred participants in the study, but is typically small—in the range of 30 to 40 patients. To see if the treatment works, most are single arm studies and involve only the primary treatment, while others are smaller randomized studies with different dosages to get hints of possible early drug activity.
- **Phase III** gathers more definitive results by determining benefits and risks in a larger number of people. Hundreds or thousands more people are enrolled, and treatment results are measured against placebo or existing treatments.
- **Phase IV** occurs after the FDA approves the medication and it becomes available to the public, usually by prescription. This phase examines long-term effectiveness and side effects.

### Safety First

To ensure the safest possible situation for participants, clinical trials must be approved and monitored by an institutional review board (IRB), an independent committee composed of doctors, researchers, and patient advocates. IRBs also ensure ethical practices. Participants must be well

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informed about their rights, including the right to withdraw at any time. Rules are strict. IRBs stop studies if side effects are common or dangerous.

The IRB also can halt a study if a treatment proves so beneficial that it should be made available to the control group—and the public—as soon as possible.

**Risks and Rewards**

Adrian Dobs, M.D., Professor of Medicine and Director of the Johns Hopkins Clinical Trials Unit, stresses, “People generally do better when they enroll in a study. They receive excellent healthcare, perhaps otherwise unavailable, including learning about diet and lifestyle.” Dr. Dobs points out that often participants are followed much more closely than in regular clinical practice and may receive advanced and expensive testing, such as magnetic resonance imaging. Often, underlying conditions are diagnosed that might not have been found otherwise. Moreover, the majority of trial patients “feel more motivated, exercise more, and take their medication regularly because they know they are being observed,” says Dr. Dobs.

Clinical trials, though, are at their core *experiments to discover through careful observation what cannot be determined by reason alone*. Simply stated, the medication or procedure is still in development, so there are no guarantees that the therapy will work or that it won’t cause unpleasant or even harmful side effects. Dr. Dobs explains that the most distress is caused by side effects, which can range from relatively mild symptoms, like dry mouth, to severe impairments, such as a heart attack. The experimental treatment may also prove less effective than current standard therapy. Participants may become frustrated by having their hopes raised for a treatment that turns out to be ineffective.

What’s more, even if a drug works well, you may be distressed to learn that it is unavailable at the trial’s end because it still must complete the lengthy FDA regulatory process before it is approved for the public. On the other hand, you may discover after all is said and done that you’ve been in the placebo section of the trial.

With so many uncertainties, no one is enrolled before signing a lengthy and detailed consent form. The document details the purpose, risks, and benefits of the study. In addition, most researchers will take as much time as necessary to answer all of your questions and make sure that you completely understand how the study works and what is expected of you. If you decide to join a study, be sure you understand the details completely before signing, and keep a copy of the document for review.

**The Role of Placebos**

A common misunderstanding by people enrolling in trials concerns the use of placebos— “dummy” or “sugar” pills with no active therapeutic ingredient. People generally assume that enrollment in a clinical trial means they will receive the investigative treatment. This isn’t the case. Half the participants are usually assigned to a control group for comparison with the new treatment, and this group receives either a placebo or the current standard treatment.

The gold standard of clinical trial design is a randomized, double-blind study, where participants are placed in the placebo or treatment group by chance, and neither the patient nor the doctor knows who is getting what. This is to control for the “placebo effect”—people who feel better because they

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think they're taking real medication even though they've been given sugar pills. The good news is that studies demonstrating this effect highlight the important role a patient's attitude can play in the healing process. However, it can also keep researchers from knowing how well a new drug is working. Randomized enrollment helps ensure results are not biased by participant expectations.

### **Before You Enroll**

- Prior to enrolling, you should be able to answer the following questions:
- Who is funding the trial?
- Why do researchers think the treatment may work?
- Will the treatment cause any pain? If so, for how long?
- What happens if the treatment is harmful?
- What medications, procedures, or treatments should be avoided during the trial?
- Will trial results be made available to participants and others?
- Can the treatment be continued after the trial is over?
- What are the possible short- and long-term side effects?
- How do the risks and benefits of the investigative treatment compare with proven available treatments?
- What costs will be covered by the trial (for travel or overnight stays, for example)?
- Will there be any remuneration?
- Will participation affect insurance or medical coverage?

### **Finding a Clinical Trial**

To find a trial, contact your local hospital or medical center, or ask your doctor to help. Be wary of claims in advertisements, and make sure your health costs are covered. The following sources list open clinical trials at Johns Hopkins and elsewhere and also address important questions:

- The James Buchanan Brady Urological Institute, The Johns Hopkins Hospital, 600 N. Wolfe Street, Baltimore, MD 21287-2101; <http://urology.jhu.edu>.
- The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, 1650 Orleans Street, Baltimore, MD 21231-1000; [www.hopkinskimmeltcancercenter.org/clinicaltrials](http://www.hopkinskimmeltcancercenter.org/clinicaltrials)
- Johns Hopkins University Center for Clinical Trials; 410-502-4419.
- The National Institutes of Health, Bethesda, MD 20892; 800-411-122; Website: [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
- Center Watch, Inc., Boston, MA 02210-1212; 800-765-9647; [www.centerwatch.com/patient](http://www.centerwatch.com/patient)
- Trials Central; <http://www.trialscentral.org>



## HORMONAL THERAPY FOR ADVANCED PROSTATE CANCER

**JACEK MOSTWIN, M.D., D. PHIL.,** *a professor of urology at Johns Hopkins, is head of the Division of Reconstructive and Neurological Urology. Dr. Mostwin is also the medical editor of the Johns Hopkins Prostate Bulletin.*

**I**n the ongoing war against prostate cancer, researchers are making progress. Twenty years ago, many of the men diagnosed with prostate cancer clearly had tumors that had extended beyond the prostate. Thanks to the PSA test, however, men are now being diagnosed much earlier, when the cancer is still within the prostate and they can be cured with a radical prostatectomy.

In the past, about 40% of men experienced a detectable PSA level within ten years after undergoing a radical prostatectomy. This number is dropping, and will continue to do so as more men have their cancer detected early. Still, the return of PSA after an initial prostate cancer treatment is a distinct possibility that strikes fear in every cancer patient. A rise in PSA means that a few cells escaped from the prostate before it was removed or irradiated, and have now grown to the point where they've produced enough PSA to raise concern.

What to do when the PSA becomes detectable? The good news is you may not need to do anything for years.

This may come as a surprise to many prostate cancer survivors who feel the best course of action for recurrent cancer is immediate treatment. But men need to understand that at this point there is no known cure. Frequently, physicians recommend (or patients request) starting hormone treatment to reduce PSA. This does not cure the disease and is sure to impact adversely on a man's quality of life.

The optimal time for initiating hormonal therapy remains unknown. In general, treatment is given when the cancer has spread to other areas of the body, such as the lymph nodes, liver, lung, or bones; when the patient is wracked with bone pain; or when there is a large mass of cancer obstructing the kidneys or bladder. In such cases, radiation therapy is used to control local symptoms, such as bone pain, caused by metastasis.

Hormonal therapy is very effective in causing a remission, improvement in pain, and reduction in tumor mass and PSA levels for some time. Unfortunately, most patients eventually develop resistance to treatment and the cancer grows again.



The following questions are ones that I am frequently asked about the use of hormones for prostate cancer that has returned.

**Q.** What are the types of hormonal treatment?

**A.** Surgical removal of the testicles (castration, or orchiectomy) or regular treatments with drugs that reduce the production of testosterone, the fuel that stimulates tumor growth, will have immediate effects. There are several types of hormone therapy currently used today:

**Orchiectomy:** This is an outpatient procedure to remove the two testicles. This form of surgical castration immediately eliminates the main source of male hormones and produces a rapid decline in hormone levels. This procedure is very effective and relatively inexpensive, but irreversible. There is no difference in effect or survival for patients taking hormones compared to those undergoing orchiectomy.

**LHRH agonists:** The use of luteinizing hormone-releasing hormone (LHRH) agonists is a form of “chemical castration” that prevents the testicles from producing testosterone. Commonly used injectable LHRH agonists include leuprolide (Lupron) and goserelin (Zoladex), and these are taken every one, three, or four months, depending on the extent of the cancer.

Viadur is an implantable version of leuprolide that provides continuous therapy for a year without the need for regular injections. Sexual function will be eliminated soon after a patient begins on LHRH agonists, but can return when the drugs are stopped.

**Female hormones:** The female hormone estrogen (diethylstilbestrol, or DES) is taken to stop the testicles from producing testosterone. DES usage declined significantly after the discovery of LHRH agonists because of its side effects (such as increased blood clots in the legs and increased risk of heart attack and stroke). Some patients may benefit from lower doses of this inexpensive drug.

**Antiandrogens:** After orchiectomy or treatment with an LHRH agonist, the body no longer gets testosterone from the testicles. However, the adrenal glands still produce small amounts of male hormones. Adrenal androgens have little effect on the prostate. Sometimes, a doctor may then prescribe an antiandrogen, an oral medication that blocks the effect of any remaining male hormones. When used with an LHRH agonist, this combination of treatment is known as a total androgen blockade. Research has shown that total androgen blockade does not offer any major advantage over LHRH agonists or orchiectomy.

Total androgen ablation is frequently used for a short time (about four weeks) in some cases during the initial phases of LHRH treatment. The antiandrogen is used initially to block a surge of testosterone that occurs in the first week after beginning LHRH agonists). Also, it is used in cases where there is early evidence of relapse after LHRH monotherapy or bilateral orchiectomy.



The role of antiandrogens alone without orchiectomy or LHRH agonists remains unclear. It is becoming increasingly common to use them as single agents prior to the development of metastasis in patients with high risk for tumor recurrence after local treatments. Unfortunately, no studies to date show that antiandrogen treatment administered on an adjuvant basis will prolong the survival of men with prostate cancer. It is also possible that if the tumor progresses after antiandrogen “monotherapy” it may not respond as well to LHRH agonists or orchiectomy.

Commonly used antiandrogens include flutamide (Eulexin) and bicalutamide (Casodex).

**Q. How does hormonal therapy work?**

**A.** Hormonal therapy—also called hormone or androgen deprivation, or hormonal or androgen ablation—is effective at turning off the body’s supply of male hormones, which prostate cells need to grow and develop. When the supply is shut off by drugs or by removing the testicles, a portion of the cancer dies, tumors generally shrink, and PSA levels drop. Not having a hormone supply can set back proliferation of prostate cancer cells for years. Unfortunately, it is not a lethal blow because prostate cancer is heterogeneous, which means it’s actually made of a variety of cells.

Some of the cells are resistant to a hormone treatment that targets only one kind of cell and they continue to grow in the absence of male hormones. These are called androgen-independent or androgen-insensitive cells. Cancer that seems to defy hormonal therapy altogether is called hormone-refractory disease.

**Q. When should hormonal therapy be started?**

**A.** The question of the exact time to start hormonal therapy has led to a lot of debate within the oncology community. If you have a cancer that has not spread to the bone and there is no sign that anything is wrong except a rising PSA, there is no conclusive evidence that immediately starting hormonal therapy—the mainstay for 50 years in slowing the disease—will prolong life.

The Veterans Administration Cooperative Urological Research Group study reported in 1973 that there was no difference in survival between men who started hormonal therapy early in the course of prostate cancer and those who started treatment when they had bone pain from the cancer.

More recent studies conducted in England have shown that while not prolonging survival, early hormonal therapy reduces the incidence and severity of symptoms and complications associated with prostate cancer: pain, urinary blockage, and pressure on the spinal cord. The important issue is that the cells that eventually prove fatal are the hormone-insensitive cells, and treatment has no effect on them, no matter when the therapy is started.



While it seems to make sense intuitively, there are no data to support that initiation of androgen ablation much before documented evidence of metastasis (or perhaps at a predetermined time that will indicate a reasonably high risk) will prolong survival of men with prostate cancer.

If a man's cancer has recurred but has not metastasized, he should adopt more conservative strategy regarding initiation of hormonal therapy. This entails being monitored closely by a physician so hormonal therapy can be started when there is evidence of metastasis or when the risks for metastasis override the risks for side effects of hormonal ablation. Every six months the doctor should administer a PSA test to track disease progression; check for any increase in the size of tumor; and perform a serum creatinine test to make sure kidney function is not being impaired.

The doctor should also order a bone scan once or twice a year to find out if the cancer has spread to the bone.

Current research is focusing on identifying risk factors and predictors to help us define how fast the cancer is growing. This will help doctors to make sensible decisions about how imminent metastases are. This may help us to decide to treat before metastasis occur.

### **Q. What are the side effects of hormonal therapy?**

**A.** In general, hormonal therapy will cause significant side effects after several months of treatment. This is especially important for patients who have no symptoms. Long-term side effects of hormone use may include one, some, or all of the following:

- Decrease in mental acuity
- Loss of muscle mass
- Decreased energy
- Loss of sexual function
- Osteoporosis
- Depression
- Anemia

These factors need to be taken into consideration in making your decision about when to begin hormonal therapy. In addition, "hot flashes" (also called "flushes") occur in two-thirds of men who receive drugs to inhibit the production of male hormones, and in half of the men who have undergone an orchiectomy.

These hot flushing episodes include feelings of increased warmth in the upper body and face. The skin may also redden and sweating is common. The episodes occur without cause, and may last for just seconds, but for many men they continue for several minutes. For some, the incidence of hot flushes decreases over time, but unfortunately in other patients the flushing continues unabated for years.



## Advice to Help You Cope With Side Effects of Hormonal Therapy for Prostate Cancer

Hormonal therapy for prostate cancer can be rough with unpleasant side effects. The following advice may help soften the impact.

The male hormone testosterone influences more than a man's sex life. It also plays a role in bone health, muscle mass, levels of energy, and even psychological well-being. Hormonal therapies for prostate cancer, known as androgen-deprivation therapy, shut down testosterone production. When testosterone levels plummet, the effects are swift and unpleasant.

Knowing what side effects can be expected with androgen-deprivation treatments, and the strategies that help relieve them, can provide a useful perspective for conversations with your doctor about your prostate cancer treatment options.

### Is Intermittent Treatment the Answer?

Prostate cancer specialists continue to look for new ways to reduce or compensate for the side effects of androgen-deprivation therapy. A relatively new approach is intermittent therapy. In this type of treatment, which is still being evaluated for effectiveness, the anti-androgen agents are given until prostate-specific antigen (PSA) levels drop. At that point, the treatment is stopped and not resumed until PSA levels rise again.

This strategy gives prostate cancer patients a break from treatment side effects. Some evidence suggests that intermittent therapy also may slow the development of hormone-refractory prostate cancer, in which the cancer cells become resistant to hormone treatment. Early studies suggest that intermittent therapy for prostate cancer may be as effective as traditional treatment.

### Help for the Big Three

The three most common side effects of androgen-deprivation therapy are hot flashes, loss of libido (sex drive), and erectile dysfunction (ED). Because ED and loss of libido are inevitable consequences of this prostate cancer treatment, it's important that couples know what to expect beforehand. ED drugs -- Viagra (sildenafil), Levitra (vardenafil), and Cialis (tadalafil) -- and mechanical devices can be used to treat ED, but they have no effect on libido. Counseling with a sex therapist can help couples to explore their needs and expectations and to sort out the emotional issues related to their changing sexual relationship.

The hot flashes familiar to postmenopausal women can be just as disruptive and frustrating for a man. They can interfere significantly with nighttime sleep, which in turn affects mood, energy level, and cognitive ability the next day. The antidepressant Effexor (venlafaxine) or the anticonvulsant Neurontin (gabapentin) will relieve hot flashes in some men.

### More Side Effect Strategies

Androgen-deprivation therapy for prostate cancer is associated with a range of other side effects. These strategies may help reduce the side effects:

- **Weight gain.** Men on androgen-deprivation therapy for prostate cancer typically gain weight. Working

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with a dietitian from the outset and establishing a routine of regular aerobic exercise, like walking, can help keep weight under control.

- **Muscle mass.** Testosterone plays an important role in building and maintaining muscle mass and strength. A regular program of strength training can help preserve both.
- **Anemia.** Anemia is common among men on androgen-deprivation therapy for prostate cancer. If anemia is severe, a medication called Procrit (epoetin alfa) or Aranesp (darbepoetin alfa) may be prescribed.
- **Bone loss.** Suppression of testosterone significantly decreases bone mineral density and increases the risk of fractures. Getting sufficient calcium and vitamin D is important, as is regular weight-bearing exercise such as walking. It's also important to not smoke and to reduce your intake of alcohol and caffeine. The osteoporosis medications Fosamax (alendronate) and Actonel (risedronate), as well as estrogen supplementation, also help to prevent and treat osteoporosis.
- **Zometa.** For men whose prostate cancer has spread to the bones, an injectable medication called Zometa (zoledronic acid) will help prevent fractures and other bone complications. Zometa can provide significant pain relief as well.
- **Breast enlargement.** Breast enlargement (gynecomastia) is a common and embarrassing side effect of androgen-deprivation treatment for prostate cancer. Irradiation of the breasts before treatment may reduce the likelihood that this will happen.
- **Fatigue and lack of energy.** Restful sleep, strength training, and aerobic exercise can help both problems. For men who are depressed, treating the depression also may reduce fatigue and listlessness.
- **Depression.** Prostate cancer patients may be depressed for a variety of reasons, including the effects of androgen deprivation. Daily exercise and adequate sleep can improve mood, but if depression is severe or long lasting, a prescription antidepressant may be needed.
- **Cognitive changes.** Many men complain of memory problems or other cognitive difficulties during prostate cancer treatment. Some research suggests that giving men supplemental estrogen improves some types of cognitive functioning.
- **Insulin resistance.** In a study conducted at Johns Hopkins, researchers found that men treated with androgen-deprivation therapy for prostate cancer for at least a year have more insulin resistance and higher glucose levels than do healthy men or men who have been treated with surgery or radiation. In fact, 44% of the men in the study had glucose levels above 126 mg/dL (the cutoff point for a diagnosis of diabetes).

Insulin resistance and diabetes also are significant risk factors for heart disease, stroke, and other serious medical conditions. The researchers recommend that men who are on long-term androgen-deprivation therapy be screened for diabetes and treated if necessary.



**Q. Whose decision is it to begin hormonal therapy?**

**A.** The process begins with a conversation between doctor and patient. The doctor should convey to the patient all the reasons why hormone therapy should be started and what the goals of the treatment are.

Many physicians today may find it difficult to deal with men who have a biochemical relapse—a rising PSA. Doctors may not fully realize the extent to which patients are constantly concerned about rising PSA, even minimally rising PSA. Doctors are not sure what this means in terms of final outcome. Our culture is such that we want to do something, so doctors and patients often opt for the early use of hormones.

It is very difficult to admit that in some instances, this decision may be hastened by a substantial, unspoken financial incentive on the part of the doctor. Some forces within the pharmaceutical industry have been too aggressive in encouraging doctors to prescribe hormones and were fined for doing so by the FDA.

Hormonal therapy is a very effective treatment; however, it is not curative, and the benefits, though sometimes long lasting, are nonetheless usually temporary. A man should always question his doctor:

- What exactly are you planning to accomplish with hormonal therapy?
- Will the cancer-fighting benefits offset the quality-of-life negatives?
- Will I live longer?

Remember that lowering PSA with hormones doesn't always mean you are going to live longer. For instance, researchers from Johns Hopkins conducted a large study of approximately 1,400 men in which they compared the survival of men who received orchiectomy plus flutamide (Eulexin) to that of those who received orchiectomy plus placebo. They reported that the men who received orchiectomy plus flutamide (total androgen ablation) had a 15-percentage-point higher incidence of PSA normalization. This represents over 100 patients.

One would expect that if PSA normalization reflected a major benefit, that there would have been a prolongation of survival. There wasn't. We now know that certain drugs may "shut off" the PSA gene and this may not reflect an effective anti-tumor effect. In addition, androgen blockade may reduce the amount of PSA made by the tumor cells but others may keep growing unabated.

**The bottom line:** If you are not satisfied with what you hear from your physician, seek a second opinion.



**Q. How long should hormonal therapy be used?**

**A.** For patients with metastatic cancer, the therapy is used indefinitely as long as it can control the progression of cancer.

When a man eventually starts hormonal therapy, the early results are generally so encouraging that he may mistakenly think that the cancer has been defeated. The tumor shrinks, PSA levels drop in the blood, and the patient feels better, at least psychologically. But only the hormone-dependent cancer cells have been affected, while cancer cells not affected by the hormones continue to grow.

How long do hormones or an orchiectomy keep the cancer at bay? The time frame varies from man to man. Over time, however, the deadliest cancer cells survive and thrive because they are impervious to all available therapies. In the past, 10% of men who started hormone therapy when they had metastases to bone lived less than six months and 10% lived longer than ten years. The other 80% fell somewhere in the middle. Studies have shown that half survive three years or less and that 25% are alive after five years.

**Q. What are the benefits of intermittent hormonal therapy?**

**A.** Intermittent hormonal therapy is used because some doctors believe constant exposure to hormonal drugs might promote resistance. They recommend the on-and-off use of hormones as an alternative. With intermittent therapy, hormonal drugs are stopped after a man's blood PSA level drops to a very low level and remains stable for a pre-determined amount of time. Once the PSA level begins to rise, the drugs are started again.

The advantages of intermittent hormone therapy are a reduction in the side effects of the hormone therapy during the periods that the patient is off treatment, and reduced overall costs. Early studies have suggested that success in treating the cancer is not impaired by using intermittent therapy, but intermittent therapy is still investigational. The amount of time one needs to be on treatment and the exact time to restart treatment if the cancer returns have not been established. Also, it is not known whether intermittent therapy is better than no treatment or continuous hormonal treatment.

I currently have some patients on the intermittent approach. Their PSA rise was usually very rapid—from 2 ng/ml to 25 ng/ml to 45 ng/ml, for example—and in such situations I have recommended a short course of hormones because, in our experience, bone metastasis may develop very rapidly (within months). Hormonal treatment is continued until the PSA decline is sustained for about six months.

I may then recommend that the patient consider a clinical trial, with new compounds when his PSA begins to rise again. Our preference is to use compounds (chemotherapy) that will attack both androgen-sensitive and androgen-insensitive cells and, we hope, kill them off.



**Q. What's the latest thinking about hormonal therapy for prostate cancer?**

**A.** I think we now have an understanding of what we can get from hormonal therapy in terms of clinical benefits. We have different modalities of treatment, different approaches. We know what the target is: a simple suppression of testosterone.

One of the major focuses in prostate cancer research now is to find out why the cancer becomes resistant to hormonal therapy. What we don't know very well are the mechanisms by which patients become resistant to hormonal therapy. Why does the treatment fail? What types of mechanisms are responsible for this resistance? Are the resistant cells different from those that are sensitive to hormones and, if so, how can we identify them?

Hormonal therapy does work. If you evaluate what happens to patients with advanced disease you will see that there is a clinical benefit for many who undergo androgen ablation, which is the treatment designed to block production of male hormones. It will delay the progression of disease for many of them. It certainly slows down the process of spread for a while, until the cancer cells become resistant.

Despite this, experts doubt that the proportion of cancer cell kill that can be accomplished by hormonal therapy is sufficient to make patients live substantially longer while enjoying a better quality of life.

**Q. What should be done when hormone therapy fails?**

**A.** If you want to attack cancer aggressively, don't pin your hopes just on hormones. As hormones begin to lose their effect on the tumor and PSA begins to rise yet again after a course of therapy, consider enrolling in a clinical trial aimed at killing cancer cells that hormones can't touch. As a trial participant, you will receive the latest medication or cutting-edge therapy provided by top specialists at leading health-care facilities.

If you're a terminally ill patient, the clinical trials available may be limited, but they can offer a real source of hope—and they may provide significant improvement in pain relief and functional status. For information about prostate cancer clinical trials being conducted at Johns Hopkins, see page 8.



## Advanced Prostate Cancer and Worsening Anemia

There is a lot of research under way into methods for suppressing and killing cancer cells that have made their presence known following prostate cancer surgery or radiotherapy. Learning how to successfully battle recurrent cancer involves not only unraveling the secrets of cell biology, but also learning all there is to know about the physiology of the patient with advanced cancer.

At a recent AUA meeting, researchers from the Oregon Health & Science University (OHSU) Cancer Institute and the Southwest Oncology Group (SWOG) presented the first study demonstrating a relationship between hemoglobin change during treatment and survival for men with advanced prostate cancer.

Androgen deprivation, or hormonal therapy, is the standard treatment for prostate cancer that has spread beyond the gland. This therapy blocks the production of male hormones that can promote prostate cancer growth. This common treatment for advanced prostate cancer wipes out most male hormones found in the body. It also is known to reduce red cell production, making anemia one of its adverse effects.

The OHSU scientists identified a new method of determining how men with advanced prostate cancer will respond to treatment, be it hormone therapy, chemotherapy, or radiation. Their major finding: Worsening anemia during the first three months of hormonal therapy for metastatic prostate cancer predicts shorter survival and earlier relapse.

Anemia is common among newly diagnosed prostate cancer patients with metastatic disease—approximately one-fourth of these men are anemic. Previous studies have shown that men who are anemic before treatment experience shorter survival and are prone to early relapse. One recent study has shown that a decrease in hemoglobin after one month of treatment is predictive of early relapse in men with high-risk prostate cancer that has not spread.

“These results suggest that by monitoring anemia during the first three months of treatment, we can provide men with a better idea of how well they will fare,” said principal investigator Tomasz Beer, M.D., Director of the Prostate Cancer Research Program at the OHSU Cancer Institute.

“Relatively little was known about hemoglobin change after the beginning of hormonal therapy for advanced prostate cancer,” Dr. Beer said. “We were interested in learning how changes in anemia during early treatment impact survival for these men, because there are ways of treating anemia. There may be opportunities to study whether treating anemia would improve survival, making it a modifiable risk factor.”

Dr. Beer and his colleagues tested this hypothesis in a retrospective analysis of SWOG 8894, a randomized study of orchiectomy (surgical castration) versus orchiectomy plus flutamide (Eulexin) in previously untreated metastatic prostate cancer.

Of the 1,286 subjects enrolled in SWOG 8894, data from 817 subjects were available for this analysis, which included a number of other traditional risk factors beyond hemoglobin, including Gleason score and disease extent.

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## ADVANCED PROSTATE CANCER TREATMENTS

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### **Advanced Prostate Cancer and Worsening Anemia (continued)**

The median pretreatment hemoglobin was 13.7 g/dl before treatment and 12.8 g/dl after treatment. Overall, the mean change in hemoglobin between the baseline measurement and three-month follow-up was a decrease of 0.54 g/dl.

Patients whose hemoglobin levels dropped 1.6 g/dl or more during that period had a 31% higher risk of death than did those whose hemoglobin increased by more than 0.3 g/dl.

“We now know that baseline hemoglobin and three-month hemoglobin change are prognostic, even after taking into account these other risk factors,” Dr. Beer said. “Further study is needed to fully understand the underlying biology of this affect and to determine if reversing anemia can improve survival in patients with advanced prostate cancer.”

Metastatic prostate cancer affects the body in many different ways, as Dr. Beer’s study has pointed out. If you have metastatic prostate cancer, be sure to review your current hemoglobin levels with your doctor.



## CHEMOTHERAPY FOR RECURRENT PROSTATE CANCER: THE BEGINNING OF A NEW THERAPEUTIC ERA

**MICHAEL A. CARDUCCI, M.D.**, *Associate Professor of Oncology and Urology at Johns Hopkins, is Co-Director of the Drug Development Program at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins.*

**P**rostate cancer is highly curable when diagnosed early, before it spreads beyond the prostate. More men than ever before are being identified and treated at this early stage thanks to regular screening with a digital rectal examination (DRE) and a blood test for prostate-specific antigen (PSA), the enzyme that is usually elevated in the blood of men with prostate cancer. That's the good news.

The bad news is that upwards of 30% of men have their PSA rise again at some point after surgery or radiation treatment, a signal that some cancer cells have been left behind and are multiplying.

By 2015, new prostate cancer diagnoses are projected to reach 300,000 a year. Prostate cancer is now the third most common cancer in men. It is estimated that almost 29,000 men will die from their disease each year. With that grim figure as a constant reminder, researchers are hard at work developing and testing new therapies that will target the marauding cancer cells involved in prostate cancer progression and metastasis, hoping to keep them from multiplying, killing as many of the cells as possible in the process.

More than three decades ago, chemotherapy was tried in an effort to delay the progression of advanced prostate cancer, but the results were extremely disappointing. This was due in great part to the fact that the drugs being used were not designed for prostate cancer. The therapy was offered to men who had failed all other treatments. These patients were already suffering from pain and weakness, and chemotherapy was their last chance at survival.

However, that was yesterday's approach with chemotherapeutic agents. Thankfully, we are now in a new era. With the FDA approval of the injectable cancer drug Taxotere (docetaxel, Sanofi-Aventis) for prostate cancer in May 2004, and the publication of the landmark phase III TAX 327 study in *The New England Journal of Medicine* (October 7, 2004), we have, for the first time, a drug that has shown it not only improves the patient's quality of life (by reducing pain) but can also extend the life of the advanced prostate cancer patient.



With more than one study indicating its evidence of cancer-fighting activity, Taxotere has now defined a new standard for chemotherapy treatment for advanced prostate cancer. In at least 50% of the patients who use the drug, half will get a remission of some duration. Moreover, the drug represents a building block for other therapies that will be used in combination with Taxotere.

**Here are the most frequently asked questions I get from patients about the use of chemotherapy after cancer spreads beyond the prostate (and my answers to them).**

**Q. How does chemotherapy work?**

**A.** Chemotherapy, or drug therapy, is used to kill cancer cells in organs or in the blood while attempting to limit the damage to normal cells. Chemotherapy is useful in fighting cancer that cannot be easily detected or treated with surgery or radiation therapy and has now moved on from the original site to other parts of the body (metastasis).

While chemotherapy has been successful in the treatment of testicular cancer, Hodgkin's disease, bladder cancer, and a variety of other cancers, it has so far had little effect on prostate cancer.

**Q. What are the common chemotherapy drugs for prostate cancer currently being used?**

**A.** Seven drugs have exhibited anti-tumor effects in men with advanced prostate cancer. They include:

- docetaxel (Taxotere)
- doxorubicin (Adriamycin)
- estramustine phosphate (Emyct)
- etoposide (Vepsid)
- mitoxantrone (Novantrone)
- paclitaxel (Taxol)
- vinblastine (Velban)

**Q. How does chemotherapy fight prostate cancer?**

**A.** Every tissue in the body is made up of specialized cells that replicate, grow, and die in a predictable, controlled fashion. Cancer occurs when, for unknown reasons, some of these cells begin to multiply in a disordered way. Chemotherapy destroys these aberrant cells as they replicate.



**Q. What is Taxotere?**

**A.** Taxotere is a drug in the taxoid class of chemotherapeutic agents that inhibits cancer cell division by “freezing” the internal skeleton of the cell, which is comprised of microtubules. These are hollow tubular structures composed of the protein tubulin that help maintain the shape and movement of a living cell and the transport of material within it. These microtubules assemble and disassemble during a cell cycle.

What the drug does so well is promote their assembly but then prevent their disassembly, preventing many cancer cells from dividing and resulting in cancer cell death.

Taxotere was originally approved in the U.S. for the treatment of advanced or metastatic breast cancer after failure of prior chemotherapy, as well as for patients with locally advanced or metastatic non-small cell lung cancer.

**Q. What are the side effects of Taxotere?**

**A.** Side effects occur because as it works to kill cancer cells, chemotherapy also affects normal cells—especially in the bone marrow, hair follicles, and gastrointestinal tract. Some treatments also affect the medulla, the area of the brain that controls sensations related to nausea and vomiting. Side effects from chemotherapy vary widely from person to person.

Common side effects from chemotherapy with Taxotere can include nausea and vomiting, which are typically mild symptoms, hair loss (25% of patients will go bald), increased chance of bleeding or infection, and anemia. However, with improvements in supportive care, including anti-nausea and anti-anxiety medications, most side effects are reversible, short lived, and present only for the duration of therapy. Many are able to complete all courses of the therapy.

**Q. How do you know the Taxotere therapy is working?**

**A.** Taxotere, like hormonal therapy, kills a significant number of cancer cells, but not all of them. The population of cells that is not killed—depending on how stressed these cells become—may take a short or long time to finally return.

Decreases in PSA are an important indicator that the drug is working. However, if a man is having severe side effects or his PSA is not dropping, in six to nine weeks we know that this is not the right agent for this patient. Some other therapy needs to be initiated if the patient is healthy enough and interested in continuing with another drug.

**Q. What were the results from the TAX 327 study?**

**A.** Prior to this study, chemotherapy was reserved only for the symptomatic metastatic prostate cancer patient. In this study, 70% of the patients were without any pain symptoms.



Being in better health, they therefore tolerated the drugs better and were able to complete the course of prescribed treatment, allowing the drug to show its true benefit.

Dr. Mario Eisenberger, a Professor of Oncology at the Johns Hopkins Kimmel Cancer Center and the co-chairman of this international study, enrolled patients at 105 sites in 24 countries in 1999; most men were 65 or older. They had metastatic disease (85% had bone metastases) that was worsening despite hormonal therapy. The primary goal of the study was to see if patients with metastatic hormone-resistant prostate cancer lived longer after taking Taxotere. We also wanted to see if their pain levels decreased, PSA levels dropped, and if their overall quality of life improved. The 1,006 eligible patients with advanced prostate cancer were randomized to receive one of three treatment regimens:

- Taxotere (75 mg per square meter of body surface) once every three weeks plus daily prednisone.
- Taxotere (30 mg per square meter of body surface) every week for five out of six weeks plus daily prednisone.
- Mitoxantrone (12 mg per square meter of body surface) once every three weeks plus daily prednisone. Mitoxantrone, known by the trade name of Novantrone, is an older injectable cancer medication that interferes with the growth of cancer cells and slows their growth and spread in the body.

Prednisone is a steroid that enhances the effects of Mitoxantrone and Taxotere.

The final study results revealed that the patients taking the mitoxantrone had an average survival rate of 16.5 months compared to 18.9 months for patients taking Taxotere every three weeks, and 17.4 months in the weekly Taxotere group.

In addition, the patients taking Taxotere reported better pain relief and quality of life, as well as a higher percentage of PSA reductions of 50% or greater compared to the mitoxantrone group. A PSA decline of 50% or greater in response to therapy generally predicts a significantly longer survival compared to a decline of less than 50% for patients, no matter what treatment the patient received.

Taxotere allowed the men to feel better and live longer. The Taxotere was generally well tolerated, although some patients did experience hair loss, fatigue, diarrhea, and decreased sensation in the fingers and toes. Those in the mitoxantrone group had a higher incidence of cardiac events, mostly blood clots.

What is so important about this study is that before Taxotere, no chemotherapy drug had ever shown a survival benefit for men with advanced prostate cancer. We now have such a drug. This is a great advance, and a significant milestone in advanced prostate cancer treatment. To some, these benefits seem modest when using median numbers. Clearly, however, some patients derive significant long-term benefits.



**Q. Will Taxotere be used in combination with other therapies?**

**A.** Taxotere is now the cornerstone for most upcoming chemotherapy studies for advanced prostate cancer. Taxotere is being combined with blood vessel inhibitors and endothelin receptor antagonists in upcoming studies.

**Q. What have the oncologists learned from the Taxotere study that will influence their treatment recommendations?**

**A.** Based on the TAX 327 results, I think that the current standard of care for patients with recurrent metastatic prostate cancer should be Taxotere-based therapy. We should also try adding new agents to build upon this success and test it in patients with aggressive disease before the cancer has a chance to spread.

Taxotere is certainly not a cure. However, these study findings offer hope that earlier use of the drug, whether alone or in combination with other treatments, will result in longer survival for patients. Doctors are now thinking that the chemotherapy may be beneficial when used in conjunction with hormone ablation therapies. When the body is strong and the tumor burden (the amount of cancer in the body) is small, the chemotherapy may actually be more effective. Survival rates may significantly increase for these patients, but we will only know through upcoming clinical trials.

Since we are now seeing more men in the clinic with early disease, our thinking is that these are the men who will benefit most from Taxotere therapy in the setting of a clinical trial. Important questions do remain unanswered, however, such as:

- What is the optimal time to administer chemotherapy in patients with androgen-independent prostate cancer?
- Should chemotherapy be administered in patients at the first signs of a rising PSA?
- Should chemotherapy be introduced only when there is an objective progression of prostate cancer?
- How should the chemotherapy be sequenced over a period of months to yield maximum efficacy?

**Q. What are your initial thoughts about Taxotere as an effective agent for advanced prostate cancer?**

**A.** Patients have believed in Taxotere over the last eight to ten years and have been using it regularly. We finally have confirmation that the use extends life. At cancer centers like ours at Johns Hopkins, the results of this study will increase the frequency with which we use it, providing more patients with better chemotherapy earlier in the disease continuum, when it can work even better.



**Q. Is chemotherapy going to become a realistic option for most men with advanced cancer?**

**A.** The real issue about chemotherapy is that not everyone is going to want it. Not all patients are convinced that the 2.5 months of additional survival that Taxotere treatment might bring is meaningful. However, if you talk to a man who only has an estimated 12 to 18 months of life left, that extra time is significant. Talk to a man with a rising PSA after surgery who can expect to live another 15 years, and the additional time given by Taxotere at the end of his life may not seem important at all in the early stages of his course, but may assume greater importance as his illness develops further.

**Q. Are we now at the doorstep of the chemotherapy age for prostate cancer?**

**A.** We are right at the door. A lot more work needs to be done. Building on what we already know, we really need to develop more drugs that have even greater cancer-fighting activity. In addition, we need to enroll more men into clinical trials using these drugs.

**Q. What happens to the patient who does not live near a medical center offering the latest in cancer care?**

**A.** Unfortunately, in smaller communities, there is not a high level of expertise in the oncology field. Prostate cancer chemotherapy is relatively new and there have not been fellowship programs to help train enough doctors in the use of the newer therapies. My hope is that as more people with prostate cancer go to their local doctors, these physicians will see how important the issues are and become expert in the use of the new drugs.

To find a medical professional offering chemotherapy in your area, a good place to start your search is with your urologist or primary care physician. Ask for their recommendations. You should also contact your local branch of the American Cancer Society. They will have a listing of regional cancer centers and facilities. Prostate cancer support groups can also be extremely helpful. You may find men who have a similar diagnosis. They will know of private practice oncologists and local cancer center facilities and give you important “inside” information on what a facility or particular physician is really like.

**Q. What does the future hold in the way of drugs that will be used against recurrent prostate cancer?**

**A.** There are newer drugs that will come to market. They will be used in sequence—and many times in combination—to whittle away at the cancer, keeping tumor burden low and patients well. There are many agents that we can evaluate now, which is encouraging. We just have to figure out when they will be used in treatment to send the cancer into remission.



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**Q. What role do clinical trials play in the drug development process?**

**A.** We can't assume we now have all the answers just because we have Taxotere. What will help push the science forward at a greater pace is having more men enroll in the ongoing clinical trials of experimental prostate cancer medications.

Participation in a trial examining the effectiveness of any of these new approaches can offer hope to many patients, from those with high-risk disease to those who appear to be at the end of their life. Trial participants receive the latest medication or cutting-edge therapy provided by top specialists in leading health care facilities. In addition, by contributing to the discovery of effective new treatments, participants may help countless others lead longer, healthier lives.

If you are interested in a clinical trial, contact our clinical trial information line at Johns Hopkins (see page 8). In addition, you can also receive information about national prostate cancer drug trials by going to the site that is managed by the National Cancer Institute on the Web at <http://cancer.gov/clinicaltrials> or call 1 800-4-CANCER.

**Financial Disclosure:** Dr. Carducci has performed consulting services and received grant support from Sanofi-Aventis, the manufacturer of Taxotere.



## RADIATION THERAPY FOLLOWING PROSTATE CANCER SURGERY

**H. BALLENTINE CARTER, M.D.**, is professor of Urology, Oncology, and Director of the Division of Adult Urology at the Brady Urological Institute at Johns Hopkins.

**T**he goal of removing the prostate with radical prostatectomy surgery is cancer cure. A major advantage of this course of treatment is that, should the cancer return, it will be noted by a rise in PSA in the months to years following surgery. Of course, the return of PSA strikes dread in the hearts of radical prostatectomy patients because it means their surgery did not completely eradicate their cancer and their future health and life expectancy could be in jeopardy. Even though the procedure offers excellent cancer control for most men when it is performed by an experienced surgeon, about one third of men will nonetheless experience a detectable PSA level within a decade of surgery.

Following radical surgery for prostate cancer, can these recurrences be salvaged with additional therapy, specifically radiation? The rationale for salvage radiation therapy in men with a rising PSA after a radical prostatectomy is not an easy situation to talk about. The first thing I want to do is make a few comments about PSA after a radical prostatectomy:

- PSA should be undetectable after successful removal of all cancer.
- Clinical recurrence is virtually always preceded on average three to eight years by a detectable and rising PSA.
- At present there is no standard definition of biochemical PSA failure.

There is a problem defining PSA failure because a detectable PSA alone is not a valid surrogate for clinical relapse or overall survival. The clinical implication here is that while a lower PSA cut point may overestimate and a higher PSA cut point may underestimate a true recurrence, this could lead to unnecessary delay in treatment.

What would I consider a PSA failure? I have listed my criteria here:

- Failure to achieve a PSA below 0.2 ng/ml after surgery with conventional assays that have analytical sensitivities of 0.1 ng/ml. Dr. Craig Rogers of Johns Hopkins has shown that an average metastases-free survival is about five years from surgery for the group of men who do not achieve an undetectable PSA (<0.2ng/ml).

- A PSA above 0.2 ng/ml after achieving a PSA less than 0.1 ng/ml. Dr. Steven Freedland



of Duke University has shown that the three-year risk of PSA progression is about 100%.

The optimal therapy for PSA failure after prostatectomy is truly a clinical dilemma. The problem is that a rising PSA doesn't distinguish between incurable systemic disease versus curable, local-only disease. This is complicated by the fact that the impact of salvage radiation therapy on survival is not known. The clinical significance is that local therapy alone is less likely to change the outcome of men with distant disease, whereas delayed treatment could compromise the chance of cure if recurrence is local only.

Here are three potential scenarios where radiotherapy may be beneficial:

1. Palpable and/or biopsy-proven local recurrence.
2. Persistently detectable PSA.
3. Delayed PSA rise with no clinical evidence of disease. This is the one scenario most likely to be associated with local recurrence, and perhaps most likely to be associated with benefit from salvage radiotherapy.

There are a number of observations that favor what I would consider a selective approach to salvage radiotherapy following surgery:

- Compared to observation, immediate or adjuvant radiotherapy significantly reduced five-year rates of biochemical progression and local recurrence in a group of men where two of three men had positive surgical margins. What this means to me is that when cancer is left behind after surgery, radiation therapy may have an impact on that local disease. However, I would caution that this does not suggest that this will have an impact on overall survival or progression to metastatic disease if most of these men have micro-metastatic disease already.

- Adjuvant radiation therapy for all men with locally advanced disease would subject a substantial number of men to unnecessary treatment. In the literature, five-year PSA remission rates are in the range of 27% to 45% with salvage radiotherapy.

- The impact of radiotherapy post surgery on metastatic progression and overall survival is unknown. This one fact leads me to believe that we need to be very selective in identifying men for salvage radiotherapy.

If I were going to try to help a man decide upon salvage radiotherapy, I would pay attention to the predictors of success after salvage radiotherapy and perhaps focus on the factors associated with local recurrence only:

- A longer time interval from surgery to PSA failure.
- The absence of high-grade cancer and seminal vesicle and lymph nodal involvement.
- The presence of positive surgical margins.
- A longer PSA doubling time.



Other factors predicting PSA remission include:

- Salvage treatment before PSA reaches a higher level, perhaps 1 ng/ml to 1.5 ng/ml.
- Radiation dosages in the range of 64 Gy to 68 Gy.

When I sit down to talk to a man about the possibility of salvage radiation therapy following prostatectomy, I keep the following guidelines in mind for men who would most likely benefit:

- A delayed increase in PSA two years or more after surgery, when the PSA is in the range of 0.5 ng/ml to 1 ng/ml.
- Pathologic features that suggest local-only disease:
  1. Gleason scores of 7 or less.
  2. Seminal vesicles and lymph nodes are not involved.
  3. PSA doubling time of a year or more, suggesting a higher likelihood that there is not metastatic disease.
  4. The absence of significant co-morbidities limiting life expectancy.



## TREATING PROSTATE CANCER AFTER BRACHYTHERAPY FAILURE

**Theodore L. Deweese, M.D.**, *Professor of Radiation Oncology and Urology and Chairman of the Department of Radiation Oncology and Molecular Radiation Sciences at Johns Hopkins, lectures nationally and internationally on the topic of radiation therapy for cancer.*

**DANNY SONG, M.D.**, *is an Assistant Professor of Radiation Oncology, Oncology, and Urology at The Johns Hopkins University School of Medicine. He has published several important articles focusing on the role of radiation of the prostate for managing prostate disease.*

Brachytherapy (BRAKE-EE therapy) for prostate cancer is a form of radiation therapy that is achieved through the surgical placement of dozens of tiny permanent radioactive isotopes directly into the cancerous prostate. Brachy means “short” in Greek, and in this context it means radiation that is supplied a short distance away from the prostate malignancy.

Your doctor may also refer to brachytherapy as interstitial (“in the narrow spaces”) radiation therapy, or “seed therapy,” as the procedure is most commonly called.

*Here’s how brachytherapy works:* Permanently implanted radioactive isotopes (each one about the size of a grain of rice) are placed in the immediate area of the tumor to deliver a highly concentrated, yet confined dose of radiation over a continuous period—24 hours a day for several months. While the seeds are highly radioactive, the patient’s body is not. Most of the radioactivity is absorbed directly into the prostate.

The classic theory about how radiation destroys cancer cells is that the radiation goes through the cancer cell, causing the formation of free radicals. These are molecules or atoms with a free electron that makes them react easily with other molecules. Free radicals eventually cause the cell’s DNA to break into several pieces. After this occurs, the cells are eventually unable to divide naturally, so they die. Another popular theory is that radiation goes into the cells and triggers programmed cell death, a physiologic process known as *apoptosis* in which cells are sent messages to self-destruct.

Think of brachytherapy as a sort of “smart bomb” that blasts tumor cells while sparing the surrounding rectum, bladder, and urethra. Alternatively, imagine it as a very different type of radiation therapy, given from the inside out, rather than from the outside in as with traditional radiation therapy. Brachytherapy differs significantly from external beam radiation treatments, where powerful but short bursts of radiation are given over a multi-week period.



Brachytherapy is proving to be an increasingly popular treatment option, although it is not for everyone. In 1994, brachytherapy was the choice of fewer than 4% of men who opted for radiation therapy for their cancer. Five years later, that figure had climbed to 36%.

Some radiation experts believe that the procedure will surpass radical prostatectomy as the treatment of choice for less severe forms of prostate cancer in the near future.

Although seed therapy is the fastest-growing prostate cancer therapy, it's far from being a new prostate cancer treatment. Shortly after Marie and Pierre Curie, the wife-and-husband Nobel laureates, discovered radium in 1898, urologists began experimenting with it for prostate cancer treatment.

Since then technologically superior tools, such as transrectal ultrasonography and computed tomography (CT scan), have allowed precise measuring of the prostate and more accurate insertion of the radioactive seeds.

Quality of life issues and also convenience have entered into the brachytherapy equation. The procedure is most often performed on an outpatient basis and typically takes about two hours to complete. After a radioactive seed implant, a man can return to normal activity, including work, within one to three days, with little or no pain.

But as with all initial prostate cancer treatments, those men who have had brachytherapy still run the risk of their cancer returning. They might not have been ideal candidates for the procedure. And while radiologists do make every effort to assure correct placement of the seeds, there is the potential for a 'cold spot', inadvertent underdosing due to movement of the seeds after the procedure.

**We are often asked about brachytherapy, and specifically, what happens if the cancer recurs in the months or years after brachytherapy was performed. Here are our answers to the most frequently asked questions that we receive.**

**Q. When are PSA tests performed after brachytherapy?**

**A.** To test for the presence of prostate cancer, PSA tests are performed three months after the brachytherapy, again at six months, twelve months, and then every six months after that.

At three months, I am expecting very little change. In fact, there are some patients, especially those with irritative voiding symptoms (burning sensation upon urination), who may have a PSA that has not changed at all since before the brachytherapy.

Within two years, I expect that the PSA will drop to 0.5 ng/ml or less. Having said that, I alert my patients that it is not uncommon for the PSA not to reach this undetectable level, either because a small amount of prostate tissue remains making PSA or else the tumor has



not been completely destroyed. Therefore, what I look for is the lowest PSA level possible (nadir) and I expect that it remains there indefinitely.

**Q. What is the PSA “bounce”?**

**A.** Following radiation treatment, PSA level falls, but for some men it may then actually start to go back up—it “bounces.” While certainly upsetting for many men, this scenario is not uncommon, nor does it mean that the cancer has recurred.

PSA bounce occurs in almost 35% of men undergoing radiation treatment. The exact cause of this PSA bounce is not known. Several common activities can result in a transient PSA bounce, including sexual activity, the most common cause; rectal bleeding causes bounce, as do bike riding, horseback riding, cystoscopy, and colonoscopy. Patients should not be scared of these transient PSA changes. The PSA will eventually start to go back down.

**Q. What can be done for a man who has undergone brachytherapy if his PSA suddenly starts to rise?**

**A.** If I see three consecutive rises in PSA in any man who has undergone a cancer-curing radiation therapy, it means the therapy has not worked and cancer is coming back. At this point it doesn’t mean it’s metastatic (that the cancer has moved from the prostate to attack nearby bone), but simply that there is definite cancer activity.

Unfortunately, a seed therapy patient may not be a good candidate for “salvage therapy” with a radical prostatectomy at this time because radiation can cause scarring of the prostate and surrounding tissue, making it difficult for the surgeon to remove the gland without the risk of damage to the urethra, bladder, and/or rectum.

When cancer has definitely recurred, a man should talk to his oncologist or urologist about the need for further testing to determine the extent of the disease. These tests include a biopsy, bone scan, and three-dimensional computerized tomography (CT) scan of the abdomen and pelvis.

At this time, there are several options, including no treatment with close follow-up; you may want to consider starting hormonal therapy to reduce testosterone production (and thwart tumor growth) or a clinical trial using new, but unproven treatments, such as chemotherapy, to kill the remaining cancer cells.



## NEW THERAPIES FOR ADVANCED PROSTATE CANCER THAT MAY CHANGE THE DIRECTION OF TREATMENT

**MICHAEL A. CARDUCCI, M.D.**, *Associate Professor of Oncology and Urology, seeks to develop and evaluate new therapies for patients with urologic malignancies. Dr. Carducci's research laboratory focuses on delineating prostate cancer-specific, differentiation therapy-induced molecular pathways. These molecular pathways may lead to a greater understanding of prostate cancer growth and development and may provide new therapeutic targets for clinical testing. Clinically, Dr. Carducci conducts Phase I and Phase II clinical trials for patients with prostate, renal, and bladder cancers.*

**M**ore than three decades ago, chemotherapy was tried in an effort to delay the progression of advanced prostate cancer, but the results were extremely disappointing. This was due in great part to the fact that the drugs being used were not designed for prostate cancer. This crude chemotherapy was the last chance at survival for men who were in pain and extremely weak—poor candidates for such treatment to begin with.

However, that was yesterday's approach. Thankfully, we are in a new era, using “smart” drugs that block important molecular steps in prostate cancer cell growth. In an effort to prolong life and ease the pain of advanced prostate cancer patients, researchers have been working to find compounds that will successfully counter this deadly force. The injectable cancer drug Taxotere (docetaxel, Sanofi-Aventis) was the first agent to have a positive impact for men with advanced cancer. Taxotere is now the standard of care for men with metastatic hormone-refractory prostate cancer (see page 22).

With FDA approval of Taxotere for prostate cancer in May 2004, and the publication of the landmark Phase III TAX 327 study in the *New England Journal of Medicine*, we finally have a drug that has demonstrably improved the quality of life of the patient (by reducing pain) and can extend the life of the advanced prostate cancer patient.

Taxotere is a drug in the taxoid class of chemotherapeutic agents that inhibits cancer cell division by inhibiting the effects of Bcl-2, a protein that is thought to prevent cancer cells from dying. The drug essentially “freezes” the cell's internal skeleton, which is comprised of microtubules. These are hollow tubular structures composed of the protein tubulin that help maintain the shape and movement of a living cell and the transport of material within it. These microtubules assemble and disassemble during a cell cycle. What Taxotere does so well is



promote their assembly but then prevents their disassembly, preventing many cancer cells from dividing, resulting in cancer cell death. Once exposed to the Taxotere, these cancer cells do die.

With its reproducible evidence of cancer-fighting activity, Taxotere has now defined a new standard for chemotherapy treatment for advanced prostate cancer. *In at least 50% of the patients who use the drug, half will get a remission of some duration.* In the studies, the men who received Taxotere-based therapy lived, on average, about three months longer when compared to men who received the old drug combination of prednisone (a corticosteroid) and the cancer medication Novantrone (mitoxantrone), which was approved by the FDA in 1996 as a treatment for the pain of metastatic prostate cancer. With a survival benefit over standard treatments now proven, the use of Taxotere marks the first giant step in the battle against advanced prostate cancer.

Taxotere was originally approved in the U.S. for the treatment of advanced or metastatic breast cancer after failure of prior chemotherapy, as well as for patients with locally advanced or metastatic non-small cell lung cancer. Common side effects from chemotherapy with Taxotere include numbness and tingling of the fingers and toes. Luckily, this side effect does not often interfere with the activities of daily living. Other symptoms can include nausea and vomiting, which are typically mild symptoms, hair loss (25% of patients will go bald), increased chance of bleeding or infection, and anemia. However, with improvements in supportive care, including anti-nausea and anti-anxiety medications, most side effects are reversible, short-lived, and present only for the duration of therapy. Many men are able to complete all courses of the therapy.

Taxotere, like hormonal therapy, kills a significant number of cancer cells, but not all of them. The population of cells that is not killed—depending on how severely these cells are stressed—may take either a short or a long time to finally return. Decreases in PSA are an important indicator that the drug is working.

However, if a man is having side effects and his PSA is not dropping, in six to nine weeks we know that this is not the right agent for this patient, and some other therapy needs to be initiated if the patient is healthy enough and interested in continuing treatment.

The success of Taxotere dramatically points out that researchers are getting much better at anticipating the next move that androgen-independent prostate cancer cells will make. Thanks to the creation of bioengineered antibodies 30 years ago, and the deciphering of the human genome, researchers have been painstakingly working on a generation of targeted biological drugs that they hope will deliver the death blow directly to specific molecules, genes, or proteins that cause the cancer while cleverly avoiding nearby healthy tissue. The past decade's tremendous advances in research methods and biotechnology have led to a variety of drugs that are now leaving the laboratory for testing on human subjects with advanced prostate cancer.



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## ADVANCED PROSTATE CANCER TREATMENTS

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These experimental drugs offer oncologists alternative ways to help prostate cancer patients. Moreover, when one of the new drugs or drug combinations stops working, there will be a wider selection of other drugs with which to replace it to continue battling the cancer. Many in the prostate cancer research community believe that as these drugs become more effective, less toxic, and improve the quality of life of patients, advanced prostate cancer will one day become a chronic yet manageable disease—similar in treatment strategy to rheumatoid arthritis or diabetes—with a routine of daily medications, lifestyle modification, and regular checkups.

Granted, many men are impatient for better and faster results. Their lives depend on it, and they can't understand why progress has been so distressingly slow, especially in light of President Richard Nixon's declaration of a "war on cancer" more than four decades ago. And even when a new drug is approved, a survival benefit of only a few weeks/months can seem like a cruel joke, especially when the monthly price tag is \$5,000 or more.

Research is now aimed at developing novel chemotherapeutic agents to destroy aberrant cells as they replicate. We now have medications that are showing survival advantage and cause few side effects. More drugs than we ever imagined are now being developed and tested for prostate cancer. In addition, some drugs approved for other tumor types are being tested on prostate patients as well.

Although progress has been sluggish—that is the nature of good science— please understand that we in the research community are committed to finding solutions. We are not backing down from our enormous challenge.

### **Promising Therapies**

There are now more than 200 experimental drugs in the prostate cancer pipeline, some being tested in the laboratories here at Johns Hopkins. It will take many more years of research and testing to move them through the three mandatory FDA testing phases to get them to your doctor's office. I don't have a crystal ball that will tell me which drugs will finally make it to market, but I will now review some of the more interesting therapies currently being tested, some of which have great potential.

#### **Enzastaurin (Eli Lilly)**

Our Johns Hopkins group is working with a drug called enzastaurin (en-zuh-STAW-rin). This interesting serine-threonine kinase inhibitor is already being studied in the treatment of certain types of cancer, including non-Hodgkin lymphoma, breast, colon, lung, and ovarian. We are testing enzastaurin for prostate cancer because enzastaurin blocks certain cell signaling pathways, and may prevent the growth of new blood vessels needed for tumors to grow. We conducted a Phase 1 trial three years ago, and are now awaiting the launch of a one-year Phase III national study in the third quarter of 2008 with about 160 patients. The drug will be combined with Casodex and tested against a Casodex-only group of men.



### **Tykerb (Lapatinib, Glaxo-Smithkline)**

Tykerb (lapatinib), a new targeted anti-cancer treatment recently approved for women with advanced metastatic breast cancer, is currently being studied for prostate cancer. The drug is a kinase inhibitor that works through multiple pathways (targets) to deprive tumor cells of signals needed to grow.

The most commonly reported Tykerb-related side effects included diarrhea, nausea, vomiting, rash and hand-foot syndrome which may include numbness, tingling, redness, swelling and discomfort of hands and feet. Generally reversible decreases in heart function (that can lead to shortness of breath) have also been reported in a small percentage of patients.

### **Satraplatin (Gpc Biotech)**

For those patients who are failed by first-line chemotherapy (Taxotere), there are currently no approved second-line chemotherapy treatment regimens available. The new chemotherapeutic agent satraplatin is now being studied in combination with prednisone as a second-line chemotherapy treatment. What makes satraplatin interesting is its ability to affect DNA as well as cell growth and tumor progression.

Platinum-based drugs have been clinically proven as one of the most effective classes of anti-cancer therapies. Over the past two decades, platinum-based drugs have become a critical part of modern chemotherapy treatments and are used to treat a wide variety of cancers. Satraplatin is a member of this family of compounds. But while other platinum drugs require intravenous administration, satraplatin comes in pill form and patients can easily take it at home.

The SPARC (Satraplatin and Prednisone Against Refractory Cancer) Phase III study was launched in late 2003 to assess the safety and efficacy of satraplatin in combination with prednisone as a second-line chemotherapy in patients with hormone-refractory prostate cancer. The study trial compared satraplatin plus prednisone versus placebo plus prednisone. This trial was a multicenter, multinational, double-blind, randomized study, with the primary endpoint of the study based on disease progression (how long it takes the disease to worsen).

Preliminary results from the trial presented at the annual meeting of the American Society of Clinical Oncology held promise:

- Patients receiving satraplatin had a 35% reduction in the risk of cancer progression and a 33% reduction in the risk of pain progression.
- 7% of patients receiving satraplatin had an objective tumor response compared to 1% in the placebo group.

Even so, when the drug was proposed for FDA approval in the summer of 2007, the Oncologic



Drugs Advisory Committee advising the FDA felt the data noted above were not sufficient to warrant approval for satraplatin and it recommended a delay in approval until the drug company submitted overall survival data from the SPARC study. The fate of the drug is now uncertain.

### **Aerolysin (Prx302, Protox Therapeutics)**

Working with Samuel R. Denmeade, M.D., an associate professor of oncology at Johns Hopkins, and scientist Thomas Buckley, from the University of Victoria in British Columbia, John Isaacs, Ph.D., professor of urology at Johns Hopkins, has helped modify an extremely potent bacterial toxin called aerolysin so it can be used to kill locally advancing prostate cancer, leaving normal tissues alone.

Drs. Isaacs and Denmeade have reported that when tested on mice that have human prostate cancer, one injection of the toxin into the center of the tumor was all that was needed to lead to a dramatic reduction in tumor size. When tested on monkeys with prostate cancer, the drug produced widespread destruction of prostate tissue without any significant side effects

A Phase I clinical trial started with 24 patients with locally recurrent prostate cancer to determine safety, tolerability, and therapeutic activity of the drug PRX302. The drug was injected into men with prostate cancer that had recurred following radiation therapy. Patient enrollment was completed at Scott & White Memorial Hospital in Temple, Texas and results are expected soon.

### **AS1404 (Antisoma/Novartis)**

Angiogenesis, the medical term for the formation and growth of new blood vessels, occurs by proliferation of endothelial cells in response to wound healing, menstruation, and cancer. It was Dr. Judah Folkman of Boston's Children's Hospital who first hypothesized in 1971 that the growth of solid tumors beyond a few millimeters was dependent on a rich blood supply and that the process of angiogenesis facilitates the process of cancer metastases to distant sites. Blocking blood availability, Dr. Folkman believed, would literally starve the tumor and help restore the patient's health and vitality.

There are now several angiogenesis inhibitors—drugs that block tumor growth by cutting off blood supply—in development. At Johns Hopkins, Dr. Roberto Pili has done much of the prostate work involving angiogenesis. Right now, he is working with a vascular-targeted drug, a variant on the antiangiogenesis theme, that's called AS1404. Developed by Dr. Bruce Baguley and Dr. William Denny and their teams at the Auckland Cancer Society Research Centre, University of Auckland, New Zealand, the drug has finished Phase II trials and results are being evaluated to determine if a Phase III trial will be launched. Antisoma recently announced a world distribution agreement with Novartis.



The Antisoma drug has been described as a small-molecule “vascular disrupting agent” that selectively disrupts established tumor blood vessels in a manner that is distinctly different from that of traditional angiogenesis inhibitors. The basis for the targeting of tumor blood vessels by AS1404 is thought to lie in the distinctive features of tumor blood vessels: the capillary network is more permeable and less well organized than that of normal tissue. AS1404 acts directly on the endothelial cells that line tumor blood vessels, causing apoptosis (cell suicide).

AS1404 also acts indirectly, causing the release of von Willebrand’s factor, which leads to blood clotting and occlusion of blood vessels. In addition, it triggers a local cascade of cytokines (biochemical mediators) including serotonin and tumor necrosis factor (TNF). The direct and indirect effects of AS1404 culminate in the breakdown of the vasculature and the death of tumor cells (hemorrhagic necrosis).

### **Avastin (Bevacizumab, Genentech)**

Avastin, the first commercially available anti-angiogenesis drug, is a powerful monoclonal antibody that is being tested in a variety of cancers. Developed as a genetically engineered version of a mouse antibody that contains human and mouse components, Avastin is used along with standard chemotherapy for the treatment of metastatic colorectal cancer. The good news with Avastin is that there is already encouraging data being reported about its positive cancer-killing effects on breast and lung cancers.

There is a lot of interest in Avastin for prostate cancer. Based on a study that reported that Avastin could be safely combined with Taxotere, Genentech, the South San Francisco biotech that manufactures Avastin, has begun late-stage prostate cancer clinical trials. One is a Phase II trial sponsored by the National Cancer Institute that is studying how well Taxotere, Avastin, and thalidomide together with prednisone work in treating patients with metastatic prostate cancer.

A nationwide Phase III Avastin study (Phase III Randomized Study of Docetaxel and Prednisone With Versus Without Bevacizumab in Patients With Hormone-Refractory Metastatic Adenocarcinoma of the Prostate) has recruited 1,020 patients. The goal of the study, which began enrolling patients in February 2006, is to compare overall survival of patients with hormone-refractory metastatic prostate cancer treated with Taxotere, prednisone, and Avastin versus a group that receives similar drug therapy with the exception of Avastin.

### **Monoclonal Antibodies**

Antibodies—also referred to as immunoglobulins or gammaglobulins—are produced by white blood cells in the body called B cells. They protect us around the clock from bacteria, viruses, and foreign molecules that make their way into the body. They do this by creating specific antibodies that bind to the invading antigen (bacteria, toxin, or virus), eventually



attacking and disabling the invaders by latching onto them. A specific part of the antibody shaped like the letter “Y” attaches to the antigen (invader). Just having the antibody stick onto the antigen is often enough to disable the pathogen, or inactivate the foreign toxin.

Since antibodies are so precisely able to recognize a particular antigen and are such effective killing agents, researchers began devising ways to artificially create antibodies that would selectively seek out and attack specific types of cells. In 1975, researchers Georges Kohler and Cesar Milstein of the Medical Research Council Laboratories in Cambridge, England induced B cells in mice to produce uniform antibodies that targeted particular proteins or antigens. Since these cells were all developed from one clone of B cells that could keep churning out exact duplicates of a given antibody, they were named monoclonal (“from a single clone”) antibodies, or MABs for short. The two men were eventually awarded the Nobel Prize in 1984 for their work.

Unfortunately, the MABs initially fell short as cancer fighters. That’s because the antibodies were made from mouse cells, which the human body recognized as foreign. When humans were injected with these MABs, the subjects quickly built up an immune response to the mouse antibody. Over the past few years, however, biotech breakthroughs have helped researchers work out their problems with the MABs. Using mouse antibodies that have been genetically engineered into human antibodies, today’s MABs can slip into the body undetected by the human immune system. They’re able to identify and bind to specific target cells, interfering with their function. As already evidenced with Avastin, MABs, when harnessed with drugs or radiation, can be used to attack the targeted cancerous cells, killing them in the process.

### **AGS-PSCA (Agensys) MK721 (Merck)**

MABs already have a track record with other tumors, and I think they are a good way of delivering therapy to a prostate tumor site. At Johns Hopkins, we worked on a new monoclonal antibody with Agensys, a Santa Monica, California biotech, looking at PSCA (prostate stem cell antigen).

AGS-PSCA is a fully human monoclonal antibody directed to Agensys’ proprietary target Prostate Stem Cell Antigen, an antigen expressed at significant levels on tumor cells from the majority of patients with all stages of prostate, pancreatic, and bladder cancers. Pre-clinical animal studies using human specimens of prostate tumors have consistently demonstrated that AGS-PSCA significantly inhibits both tumor growth and metastasis.

Along with Memorial Sloan-Kettering Cancer Center in New York, we enrolled patients in a Phase 1 dose escalation study with 24 patients to make sure the various doses of AGS-PSCA are well tolerated in humans. Our data was presented in October 2007 and noted that the drug was safe and that there was some PSA stabilization.



**Note:** This Agensys molecule has since been licensed to Merck and they now have a new molecule called MK721, which is slightly different from the Agensys molecule. A Phase I study will be started soon, and Merck has an aggressive Phase II study also planned.

## Vaccines

Many scientists consider the development of cancer to be a failure of the immune system (the body's natural defense system). While the body's immune system can usually recognize the difference in molecules in the body as being "self" or "non-self," it often fails to recognize cancer cells for what they are—previously normal cells that have turned rogue—and it doesn't attack and destroy these cancerous cells as it should.

Although scientists still don't completely understand how the immune system fights cancer, they suspect that the body's natural defenses routinely clean up abnormal cells. However, because tumors arise from the body's own tissues, experts believe the immune system is not always completely adept at recognizing all of them as threats. Enter vaccines.

You are certainly familiar with the flu vaccine, which is given each year in the form of inactivated flu molecules to alert the immune system so it can quickly recognize and attack the flu when and if it is contracted. Prostate cancer vaccines, such as GVAX, which are still experimental and have not been approved by the FDA, work on the same theory. They attempt to "wake up" the immune system and put it on high alert so it responds in the presence of the lethal cancer cells and then destroys them quickly.

The unanswered question for researchers is whether these new prostate vaccines will be strong enough on their own to bring relief to men with huge disease burden. There is a strong feeling within the research community that when performing studies with the vaccines, drug companies may not be choosing the right patient population for these novel therapies. If tested only on the more advanced prostate cancer patients in the final stages of the disease, the vaccine may eventually not succeed because it is just being asked to do too much. And when the vaccine subsequently fails to halt disease progression in these patients, it may be written off as inactive or ineffective for men with highly advanced prostate cancer, and therefore discarded.

In fact, many of these vaccines may actually be better suited for men with less disease; the low-toxicity vaccine could be offered to them either following their initial prostate cancer therapy (surgery or radiation) or along with hormonal therapy or Taxotere-based chemotherapy once the cancer has recurred. Proving that this is beneficial, however, takes much more money and time—two things that are in short supply at many drug companies. According to the Pharmaceutical Research & Manufacturers of America, it currently takes 14.2 years to bring a drug from laboratory bench to pharmacist's shelf, with only 1 in 5 drugs making it through FDA-mandated clinical trials. Do you wonder what the cost is for developing an approved new drug? More than \$800 million.



Prospective drug companies are reluctant to set up their drug trials with these “healthier” early-stage cancer patients because it could be many years, and hundreds of millions more dollars spent, before they would be able to demonstrate to the FDA that the use of the vaccine helped achieve their final endpoint—delay in progression of disease. In this setting, therefore, it is unlikely that any vaccine therapy for prostate cancer is going to make it.

There are several vaccines currently in testing phases, each a little different, and they all generate a significant immune response. The problem clinically is that none have generated enough information to support their being identified as a very active therapeutic tool for prostate cancer. For instance, if you administer chemotherapy to prostate cancer patients, about 50% of them will have major PSA decline; the tumor gets smaller and pain diminishes. Of the hundreds of patients in clinical trials with vaccines, however, there have been some changes in PSA and other small beneficial changes, but they have occurred in only a handful of patients, at most. Still, it is encouraging data about survival effects that keep the prostate cancer vaccine category alive.

Here is a look at two vaccines currently being tested:

**Prostvac-VF (Therion Biologics).** PROSTVAC-VF is Therion’s investigational targeted cancer therapy designed to stimulate a patient’s own immune system to seek out and destroy malignant cells expressing PSA, the protein associated with prostate cancer. In addition to targeting PSA, PROSTVAC-VF also incorporates TRICOM, Therion’s proprietary triad of costimulatory molecules, believed to enhance and sustain a targeted immune response against tumor cells. Data from earlier studies suggest PROSTVAC-VF may induce PSA stabilization, delay time to progression, and that the vaccine is well tolerated.

I am the chairman of the prostate cancer subcommittee for the Eastern Cooperative Oncology Group. We will be conducting PARADIGM, a Phase III double-blind PROSTVAC-VF trial.

**GVAX (Cell Genesys).** The GVAX vaccine (the original research was done at Johns Hopkins) contains tumor cells that have been genetically modified to secrete GM-CSF, an immune stimulatory hormone that plays a key role in stimulating the body’s immune response, destroying prostate cancer cells in the process.

Phase II study data suggesting a 35% PSA response, and survival of 26 months, really lends credence that the Phase III study should be completed. We began the VITAL-1 study in 2005 to compare the efficacy of GVAX with that of Taxotere. That study has finished enrolling patients who have asymptomatic, metastatic hormone-refractory prostate cancer. We expect data to be available in late 2008 or early 2009. The VITAL-2 study is now enrolling patients.



## Enrolling in VITAL-2

The VITAL-2 Study is now open nationally and internationally for patients with metastatic disease and symptoms. For more information about VITAL-2 enrollment, call 1.800.648.6747 ext. 3210. You may also check [clinicaltrials.gov](http://clinicaltrials.gov) for a current list of locations with open sites.

Here is an overview of the VITAL-2 study, which will compare the duration of survival between the two treatment arms—GVAX immunotherapy or Taxotere chemotherapy. To enroll, you must be:

- Male, older than 18 years of age
- Confirmed diagnosis of prostate cancer
- Metastatic prostate cancer deemed to be unresponsive or refractory to hormone therapy
- Detectable metastases
- ECOG performance status  $\leq 2$  (performance status of 3 if due to bone pain)
- Any Gleason score
- Only one prior treatment with systemic chemotherapy
- No prior treatment with gene therapy
- Taxane-naïve (no prior use of Taxotere)
- Experiencing cancer-related pain

### Here's how the study will work:

If you are selected for the study, you will be randomized to one of two treatment arms:

**Arm 1:** Cancer immunotherapy injections in combination with Taxotere every 21 days over 10 cycles followed by monthly cancer immunotherapy injections alone for life or until a new treatment for prostate cancer begins.

**Arm 2:** Taxotere administered every 21 days and prednisone daily for 10 cycles.



## HOW TO BEST PRESERVE SKELETAL HEALTH

**MATTHEW R. SMITH, M.D., PH.D.**, *an Assistant Professor of Medicine at Harvard Medical School, is an internationally respected expert on bone and secondary bone cancer due to prostate cancer. He is Director of Genitourinary Medical Oncology at the Massachusetts General Hospital Cancer Center in Boston.*

**F**ighting prostate cancer once it has returned is an enormous battle, pitting you and your physicians against a lethal onslaught. Therefore, first and foremost, you have to take total control of your health and learn all you can about the upcoming battle, as well as all the possible battle scenarios you may be confronted with in the coming years.

Since bone is a primary attack site for metastatic prostate cancer (cancer that has spread beyond the prostate to a distant site such as lymph nodes or bone), the focus of this article is bone and what can happen to it once your cancer recurs. Many prostate cancer patients are now living longer thanks to breakthrough cancer treatments, but only scant attention is paid to the fact that these therapies can also do great harm to bone. Unfortunately, the hormonal therapy and chemotherapy used to treat prostate cancer can rob bone of its precious mineral density, its ultimate strength, leading to an increased risk of bone fractures, pain, and other skeletal-related events (SREs).

Bone is critical to our survival and our bones perform several important functions. In addition to providing the body's framework and acting as the attachment point for muscles, they also protect our organs and store and release minerals vital to bodily functions, while the marrow within bone produces blood cells.

Bone, unfortunately, is one of the most popular destination sites for prostate cancer cells that are metastasizing from the prostate to a distant site. On arrival, these invading cancer cells begin a systematic process of weakening and damaging the bone. That's because bone is a rich storage deposit of substances that act like a fertilizer and enhance the growth of prostate tumor cells.

When cancer reaches the bone, a vicious cycle begins. The tumor cell produces special substances that speed up the normal ongoing breakdown of bone. In turn, the destruction of normal bone triggers the release of additional substances that encourage the growth of more cancer cells.



Knowing all you can about your bones is extremely important because what you and your doctor ultimately decide to do can make a difference not only in the quality of your life, but possibly, in your ultimate survival.

Your oncologist and urologist should aggressively protect bone. They should look for bone loss (osteoporosis) and prevent it—rather than letting it occur—as a strategy to stave off future bone metastases and painful skeletal-related events (SRE) such as falls, fractures, and cervical compression. It is estimated that once a patient experiences his first SRE, subsequent SREs occur more frequently, averaging one every three to four months.

Although many physicians choose to ignore bone issues, focusing their attention instead on the prostate cancer itself, this is a mistake. More than 100 years ago, Stephen Paget, the British physician and author, recognized the critical interplay between bone resorption and cancer cell growth. He wrote, “When a plant goes to seed, its seeds are carried in all directions, but they can only grow if they fall on congenial soil.”

Bone is certainly “congenial soil” for the prostate cancer cells. A greater understanding of this phenomenon is needed within today’s prostate cancer community if progress is to be made in the prevention and treatment of bone metastases—the unfortunate consequence of recurrent prostate cancer for many men.

Patients, as well as their physicians, need to become more “bone aware” and develop a better understanding of how both cancer and treatments prescribed to slow cancer growth can also affect bone. The bad news is that hormonal therapy for recurrent cancer can cause osteoporosis. The good news is that this is one of the side effects we can treat. Remember: It’s never too late to begin taking steps to maintain optimum bone strength.

**Q. When should men concern themselves with their skeletal health?**

**A.** If a man has a negative bone scan and rising PSA, and is about to begin hormonal therapy with a luteinizing hormone-releasing hormone (LHRH) analogue such as Lupron or Zoladex, or if he’s to undergo surgical castration, the rate of bone loss will eventually increase and may lead to osteoporosis in some men. It’s very important, therefore, that the doctor discuss with the patient the role of bone and the possibility of bone damage due to treatment and tumor burden. A plan to protect bone density should be discussed at this time.

I advise my patients right from the start: I want you to start thinking of your skeletal health. I want your bones to be as strong as possible because somewhere down the line, if the cancer spreads, or if you have to start certain medications to slow the growth of your cancer, your bones may be affected. By maintaining your bone from the outset, we may maximize your quality of life.



**Q. How do bones stay strong?**

**A.** Bone is a complex tissue that provides support for your muscles, protects vital organs, and acts as the storehouse for calcium, the mineral essential for bone density. More than 90% of the body's supply of calcium is found in the bones.

Your skeleton has two distinct types of bone. Cortical bone, which is hard, dense, stiff, and designed to withstand stress, makes up about 80% of the skeleton. Cortical bone is found on the outer shell of most bones, your hip, and in the long bones of your arms and legs. Trabecular bone, the second type of bone, is found within cortical casings, in parts of your hips, at the ends of the long bones of your arms and legs, and in the vertebrae.

Throughout life, the skeleton undergoes remodeling, a continuous process of breaking down and building up bone. Bones remodel themselves in order to grow and to repair any minor damage that may have occurred during the day. When bones are remodeling, old bone is removed and replaced by new bone.

Remodeling starts when a variety of chemicals in the body direct bone-eroding cells, known as osteoclasts, to break down and remove bone in a process known as bone resorption. This releases small amounts of calcium, magnesium, and phosphorous into the bloodstream. At the same time, other chemicals—the hormone estrogen, especially—send messages to bone cells known as osteoblasts, directing them to make new bone. First they fill in with collagen the tiny cavities made by the osteoclasts, and then they lay down new calcium, magnesium, and phosphorus extracted from the bloodstream until the bone surface is completely restored.

It's estimated that as much as 10% to 30% of the adult skeleton is remodeled each year, keeping the bones strong and dense. Bones achieve their maximum strength and density around the age of 20. This level remains stable for a few years and then slowly begins to decrease. On average, an adult man naturally loses about 1% of total bone mass every year. This process is speeded up dramatically when osteoporosis and bone metastases are present.

**Q. Why is it necessary to do everything possible to maintain maximum skeletal health?**

**A.** As I already mentioned, bones remodel themselves in order to grow and to repair any minor damage that may have occurred. When bones are remodeling, old bone is removed and replaced by new bone. However, this intricate remodeling process is upset by hormonal treatment or by invasion by prostate tumor.

**Q. What factors influence normal bone growth?**

**A.** Many factors influence bone growth. In brief, your daily intake of calcium, vitamin D, pro-



tein, and other nutrients affects the health of your bones. The sex hormones—testosterone and estrogen—exert a major influence on calcium uptake by bone tissue, and thus affect skeletal strength.

Physical activity also plays a role in bone growth and maintenance. When subjected to mechanical stress, bones respond by becoming denser and stronger. This stress comes primarily from weight-bearing activity, such as walking or running, in which your legs support your body weight; weight lifting also provides this type of healthy “stress” on the bones.

**Q. What is osteoporosis?**

**A.** Osteoporosis is a thinning of the bones, which makes them fragile and brittle, so that they fracture easily. While it’s about eight times more common in women, men can be affected by osteoporosis as well. There are effective treatments for osteoporosis. Osteoporosis, like hypertension, has been called a “silent disease.” You may not be aware of it until you fall and fracture a bone. Thus, prevention is the best line of defense.

About 20% of men with prostate cancer already have osteoporosis. However, one of the fastest growing osteoporosis risk groups consists of men with prostate cancer who receive androgen deprivation therapy to lower their testosterone levels. Most men with advanced prostate cancer suffer serious skeletal complications, which can be exacerbated by osteoporosis. The expanding use of these LHRH hormone-blocking therapies, which some patients receive for years, means that the problem of bone loss is becoming more widespread.

When someone falls or has an accident, the bone loss immediately becomes apparent. Even a minor fall can break a weakened wrist, forearm, hip, or vertebra.

**Q. How is osteoporosis diagnosed?**

**A.** Just as a blood pressure test can assess your risk of hypertension, a painless and noninvasive bone density test can indicate your risk of bone fracture.

Dual-energy x-ray absorptiometry, or DXA, is the most common bone mineral density test used today. For this test, you lie on a padded table for 10 minutes while a special X-ray machine scans your spine, hips, or forearm using ultra-low X-ray levels to precisely determine bone mass. This invaluable screening tool, which can detect even a one-percent change in bone density, is the “gold standard” of bone density measurement.

The score yielded by the test results tells how strong your bones are in comparison to what is considered to be a normal peak bone mass for your age group.



**Q. Are some men at higher risk for osteoporosis?**

**A.** Some men are more likely to develop osteoporosis than others. The factors that increase your likelihood of developing the disease include:

- Hypogonadism (low testosterone levels)
- Long-term hormone therapy
- Family history of osteoporosis
- Being chronically underweight or having a slight, “small-boned” frame
- Diet low in vitamins, calcium, and other minerals
- Being Caucasian or of European ancestry
- Smoking (which interferes with the maintenance of bone density)
- Drinking more than three cups daily of coffee, cola, or tea
- Prolonged used of cortisone or prednisone
- Being sedentary and not performing strength training and other forms of weight-bearing exercise.

The more risk factors you have, the greater your chance of developing osteoporosis.

**Q. What should a man do who is found to have low bone mineral density?**

**A.** The patient should consider treatment with a bisphosphonate (such as Actonel, Boniva, or Fosamax) and discuss with his doctor which bisphosphonate to use. As you will recall, there are two main cell groups in the bone. The osteoblasts make bone and the osteoclasts break down the bone (bone resorption). Both types of cells are very active, and work together to keep the bone intact and responding to stress. Bisphosphonate drugs (available in tablet form and injectable versions) slow down the process of bone resorption by shortening the life of the osteoclasts and prolonging the life of the osteoblasts, thus tilting the balance towards the production of bone.

**Q. Will every man with recurrent prostate cancer develop osteoporosis?**

**A.** Osteoporosis is not an inevitable consequence of prostate cancer treatment. In general, I recommend measurement of the bone density at baseline and then every one to two years. Some men will maintain good bone density despite ongoing androgen-deprivation therapy.

**Q. What practical measures can a man take to reduce the risk of osteoporosis, and will they help men with recurrent cancer?**

**A.** There are several practical measures, and there is no reason to think they wouldn't be helpful for men on hormonal therapy. These measures include making sure you get an adequate intake of calcium and vitamin D; eliminating bad habits (drinking, smoking) associated with bone loss; and performing regular weight-bearing exercise.



I recommend supplemental calcium at a level of 500 to 1,000 mg/day. Vitamin D is needed for the body to help absorb calcium. However, at least 20% of my patients are vitamin D-deficient because they don't get enough sun exposure, which is a main source of vitamin D. Therefore, I also recommend 400 IU daily of vitamin D. As for exercise, perform at least 30 minutes of weight-bearing exercise four times a week. Good activities include weight training, walking, running, racquet sports, and aerobics. Consult with your doctor to develop an exercise program based on your overall health and current level of fitness.

**Q. Can osteoporosis prevention measures stifle cancer growth?**

**A.** Prostate cancer selectively spreads to bone in part because the bone is fertile soil for prostate cancer growth. Therefore, strategies to maintain a normal rate of bone remodeling—osteoporosis prevention, for example—may have a two-fold benefit, that of maintaining bone integrity and making bone inhospitable to cancer cells.

**Q. Would a man with denser bone have a lesser proclivity for bone metastases than someone with less dense bone?**

**A.** This is an interesting question, but one of the most difficult to address in clinical trials. We believe that it is true, but there are no data confirming that hypothesis. This will take large trials, and it will be years before we get an answer.

Maintaining good bone health is a big advantage for men with recurrent cancer because they reduce their overall fracture risk. There also might be the additional benefit of delaying or preventing bone metastases.

**Q. What is the difference between primary bone cancer and metastatic bone cancer?**

**A.** Primary bone cancer refers to a tumor that originated in the bone. Metastatic bone cancer refers to cancer that originated in another organ—in this case, the prostate. Prostate cancer that spreads to the bones is still prostate cancer; it is not bone cancer. Prostate cancer cells look and behave the same whether they are found in the prostate or have spread to another part of the body.

**Q. Do prostate cancer cells destroy bone?**

**A.** Not directly. Rather, prostate cancer cells activate osteoclasts, and excess osteoclast activation contributes to bone destruction. This also contributes in part to the clinical manifestations of the bone metastases, which include pain and fractures.



**Q. How are metastatic bone cancers classified?**

A. There are two classifications: They can be called “lytic,” which means that they eat away at the bone; they’re classified as “blastic” when they make the bone excessively dense. Oftentimes there is a mixed reaction, with the lytic and the blastic mixed together. Most prostate cancers that spread to bone are blastic and appear on x-rays as abnormally dense bone.

**Q. When a patient has bone metastases, what are his chances of survival?**

A. For the patient with no prior hormonal treatment, the median survival is about four years, although 10% of men survive a decade or longer. I advise my patients that some men do very well for a very long time after a diagnosis of bone metastases. The major determinant of survival seems to be the duration of response to hormonal therapy. For men with bone metastases and progressive disease despite hormone therapy, survival is usually less than two years.

Chemotherapy and supportive care may be changing the natural history of the disease. These incremental advances have a good potential to improve overall outcomes.

**Q. What symptoms and signs do patients experience when they have bone metastases?**

A. When cancer cells develop in bone or spread to bone, they weaken its normal structure and this can produce a variety of SREs that contribute to disability and compromised well-being. Typical symptoms include pain and fractures.

Bone metastases can also produce compression of nerves in the spinal cord triggered by a collapse of the spinal column, which can lead to paralysis and death. Tip-offs to spinal compression include severe pain in the back that accompanies leg weakness, loss of sensation (typically starting with numbness or a tingling in the toes), difficulty walking, urinary retention, or constipation. Speak to your doctor immediately if you have any of these symptoms. An MRI scan is needed to provide details of the condition of the spinal cord and pinpoint any signs of compression.

**Q. How common is pain with bone metastases?**

A. Pain is the most common symptom of metastatic prostate cancer. It’s not one of your typical pains, such as you might experience from arthritis or a twisted ankle—this is a specific type of pain that really gets your attention. It is important to recognize bone pain and bring it to your doctor’s attention immediately because pain can almost always be relieved or controlled.

Initially, bone pain typically comes and goes, then, over time, it becomes more severe and continuous. For some, movement relieves the pain. For most people, it’s often worse at night. Not



all pain means bone metastases, of course. However, when it comes to bone pain, here's the guideline to follow: If you are experiencing pain (dull aching, or movement-evoked—for example, if you move your leg and it hurts) you haven't had before, and if it lasts more than seven days, you should contact your physician.

**Q. What are the goals when treating prostate cancer patients with skeletal complications?**

**A.** Relieving symptoms and preserving physical function are two of the most important goals. This means stabilizing bone and preventing breakdown. It's also important that pain be prevented while attempting to improve and maintain the best quality of life possible.

**Q. What are the best options available for treating bone metastases?**

**A.** I start with the use of anti-neoplastic treatments. This can include one or several of the following options: chemotherapy, hormonal and biologic therapies, radiotherapy, and the use of intravenous bisphosphonates.

Chemotherapy and hormonal therapies are generally used to treat all sites of cancer throughout the body and are not used specifically for pain management. However, when the cause of cancer pain is direct tumor involvement, anti-neoplastic treatments may produce pain relief if they cause significant tumor shrinkage.

The major goal of anti-neoplastic treatment is either to cure by complete elimination of the cancer or, if cure is not possible, to extend life and offer reduction in tumor symptoms.

**Q. Why are intravenous bisphosphonates helpful in the treatment of skeletal complications of metastatic prostate cancer?**

**A.** Zometa (zoledronic acid), the only intravenous bisphosphonate currently available for metastatic disease, provides significant benefits to patients with hormone-refractory prostate cancer. Therapy is typically administered once every three weeks in sessions that last 15 minutes.

What Zometa does very effectively is interfere with the excessive activity of the type of bone cells that destroy normal bone. And by doing that, it helps to restore, to some extent, the equilibrium between the two types of bone cells.

**Q. What are the benefits of Zometa?**

**A.** Zometa delays or prevents important bone complications including fractures or the need for surgery or radiation therapy to bone.



**Q. When should Zometa be used?**

**A.** Zometa is approved for use in men who have failed hormone therapy. A concept currently under review is the earlier introduction of Zometa at the time of the initial diagnosis of bone metastases.

**Q. How is Zometa being used to treat cancer-related bone complications?**

**A.** Zometa is being routinely used only in patients with documented bone metastases. Clinical trials are underway, however, that will determine the benefit of using bisphosphonates in adjuvant settings.

**Q. Are there side effects with Zometa?**

**A.** The side effects are modest. There may be a transient increase in bone pain for a few days. About one third of patients experience symptoms similar to the flu for a day or two. Occasionally Zometa can impair or damage kidney function. Therefore, it's important to monitor function regularly and address problems immediately if they arise.

**Q. When a patient is given Zometa, does it restore the bone remodeling process to normal baseline levels?**

**A.** It does for a time. Zometa is the most potent of all the bisphosphonates.



## TREATING THE PAIN OF ADVANCED PROSTATE CANCER

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*Pain is perfect misery, the worst of evils . . .  
—John Milton, Paradise Lost*

**W**hen prostate cancer recurs, it can migrate to nearby bone – and when that happens, it often signals the start of a painful, debilitating battle that can go on for years. Controlling pain and managing symptoms are the treatment goals for men with advanced prostate cancer. Studies over the years have reported that as many as 72% of advanced prostate cancer patients are in pain, with one study reporting that 47% of men with advanced cancer had pain that ranged from moderate to very bad even though they were being treated with pain medication. This should never be the case. We now are able to successfully treat all types of pain associated with advanced prostate cancer.

**My advanced prostate cancer patients at the Cancer Pain Service frequently ask the following questions. Here are my answers.**

**Q.** What is pain?

**A.** Pain is whatever a patient says it is. It's a subjective sensation that's different for each individual. We take our patients' reports of pain very seriously. The pain can be a result of their treatment, their disease, or both.

Chronic or persistent pain in advanced prostate cancer patients can range from mild to severe, and is present (to some degree) for long periods. This pain can be successfully controlled by medication. When severe pain that has been under control “breaks through” the regular medication, another fast-acting drug can be taken to relieve these new pain symptoms.

The pain caused by advanced prostate cancer—and not eventual death from the cancer itself—is often the aspect of this disease that patients fear most. Pain can weaken the immune



system, take away appetite, and cause the patient to suppress coughing, which can increase the risk of pneumonia. Therefore, in order to maintain a high quality of life for as long as possible, effective control of pain is essential. When pain is not adequately controlled, a prostate cancer patient may have trouble sleeping, lose his mobility, and become moody, angry, or deeply depressed.

**Q. What causes pain in men with advanced prostate cancer?**

**A.** People with prostate cancer have pain for a variety of reasons. The most common cause of the pain is from the cancer itself. Prostate cancer very often metastasizes—spreads from the site of the original tumor by means of cells transported by the blood or lymph—to bone, and that is when the pain is often first noted. It’s estimated that about 70% to 85% of patients with advanced cancer have bone metastases.

Our bones are critical to our survival, performing several important functions. In addition to providing the body’s framework and acting as the attachment point for muscles, they also protect our organs and store and release minerals (like calcium) vital to bodily functions, while the marrow within the bones produces blood cells.

Unfortunately, bone is one of the most common destinations for prostate cancer cells that are metastasizing from the prostate to a distant site. On arrival, these invading cancer cells begin a systematic process of weakening and damaging the bone. That’s because bone is a rich storage deposit of substances that act like a fertilizer to enhance the growth of prostate tumor cells.

When cancer reaches the bone, a vicious cycle begins: The tumor cell produces substances that speed up the normal ongoing breakdown of bone. In turn, the destruction of the bone triggers the release of substances that encourage the growth of cancer cells.

**Q. How common is pain with bone metastases?**

**A.** Pain is the most common symptom of metastatic prostate cancer. It’s not like the everyday aches and pains you might experience from arthritis or a twisted ankle—this is a specific type of pain that really gets your attention. It is important to recognize bone pain and bring it to your doctor’s attention immediately so that it can be relieved or controlled.

Initially, bone pain typically comes and goes; over time, it becomes more severe and continuous. For some people, movement relieves the pain. For most, it’s worse at night. Not all pain means bone metastases, of course. However, when it comes to bone pain, here’s the guideline to follow: If you are experiencing pain (dull aching, or movement-evoked—for example, if you move your leg and it hurts) you haven’t had before, you should contact your physician.



**Q. What is the goal of pain therapy for men with advanced prostate cancer?**

**A.** The goal should be to ensure adequate pain management and relief with the fewest side effects. When you strike that balance, the patient's functioning and quality of life usually improve.

We do have a large armamentarium of pain medications, and many different mechanisms by which we can deliver these drugs. There are also specially designed procedures and techniques to help control pain. That is not to say that we can guarantee complete relief of all pain, but we usually are able to control most pain and provide comfort and relief to most of the patients we treat.

**Q. Since pain is prevalent in so many cases of advanced prostate cancer, why is it often so poorly managed?**

**A.** Most every type of cancer pain can be relieved, but many men with advanced prostate cancer are not adequately treated. We are trying to reverse this trend through education of patients and healthcare professionals. We want patients and their families to realize that cancer patients can have their pain managed effectively and safely. Unfortunately, many people do not think that is possible, mainly because of their preconceived notions about pain medications.

Some patients fear that the morphine-based drugs given for pain relief will turn them into addicts. This is rarely the case. Other men fear the side effects of the drugs, which can include sedation and constipation. These can be prevented and relieved if they occur. Poorly trained doctors can also impede effective pain relief by their lack of knowledge of the appropriate medications or the proper dosages required to keep pain levels down. Some doctors are afraid to prescribe high dosages, fearing that a well-meaning, though misinformed, pharmacist will alert drug enforcement agencies. This situation can be avoided if the doctor speaks directly with the pharmacist, making clear the cancer patient's condition and the overall pain treatment plan that will be put into place.

Then, too, the patient may be at fault. Many men are not forthcoming about the pain they are experiencing. They think they should be able to somehow "tough out" the pain. They have the notion that they should "act like a man" and not use any pain medication, or else try to get by with a dose that is not adequate for continuous pain relief. Avoiding pain medication is not a sign of strength, however—in fact, it is misguided thinking. Good pain control actually makes you feel stronger and allows you to enjoy activities of daily living, including eating, walking, working, exercising, and sleeping.

**Q. How is pain diagnosed in a man with advanced prostate cancer?**

**A.** It all starts with a good assessment of the patient by the doctor. Pain can only be



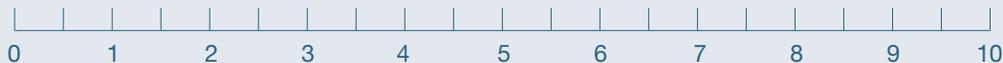
described by the person experiencing it, so the doctor needs to know when the pain started, where it is located, how long it has lasted, what the severity of the pain is, what makes it feel better, and what makes it worse. If the pain is bone pain, a bone scan or X-ray may be ordered to help pinpoint the problem sites. This step might lead to spot radiation being considered as a pain treatment option.

Pain specialists also make extensive use of pain scales (see below). I find it extremely helpful to have my patients keep a daily diary, using pain scales to rate their discomfort on a regular basis. The diary allows us to look at trends and note a particular activity that causes the pain that we might be able to modify. The diary also allows us to anticipate the pain, so medication can be taken well in advance. In addition, it lets us know how well particular medications are working and what kinds of dosage adjustments are needed.

#### NUMERICAL PAIN RATING SCALE

Please mark the scale below to show how intense your pain is.  
A zero (0) means no pain, and ten (10) means extreme pain.

**How intense is your pain now?**



#### **Q.** How is advanced prostate cancer pain treated?

**A.** Once the pain has been properly assessed, the doctor will develop a treatment plan with the patient. Pain can be treated in many ways, depending on symptoms. Sometimes the underlying cancer will be treated with a chemotherapeutic agent, which can lessen the pain. Spot radiation, in which high doses of radiation are aimed at the painful area, can also eliminate bone pain. Then there is drug therapy. The use of medication is currently the main mode of treating advanced prostate cancer pain. Drug therapy for cancer pain falls into three categories:

**Non-opioids.** These non-narcotic drugs include acetaminophen (Tylenol) and non-steroidal anti-inflammatory drugs (NSAIDs), which include aspirin, ibuprofen, and Celebrex, a COX-2 inhibitor. These medicines are used for mild to moderate pain. Concern about heart disease has recently brought use of these medications into question.



## PAIN MEDICATIONS

Here is a brief overview of currently available pain medications, their uses, and relative effectiveness.

Pain Intensity	Drug Type	Examples	Comments
<b>Mild (1-3 on pain scale)</b>	Non-opiates	Aspirin Acetaminophen (Tylenol) Celebrex Ibuprofen (Motrin) Ketoprofen (Orudis) Naproxen (Aleve)	With the exception of Celebrex, may cause stomach bleeding and ulcers
<b>Moderate (4-6 on pain scale)</b>	Weaker opiates	Codeine Fentanyl patch (Duragesic) Hydrocodone (Vicodin)	Typically used with non-opiates, which limits daily dose.
<b>Severe (7-10 on pain scale)</b>	Strong opiates	Fentanyl lozenge (Actiq) Fentanyl patch (Duragesic) Hydromorphone (Dilaudid) Morphine Oxycodone (OxyContin)	These drugs have no dosing limits and can be used as needed for maximum pain relief.
<b>Breakthrough pain</b>	Strong opiates	See "Severe" above	Some immediate-release drugs may take 45 minutes to provide pain relief, while Actiq, an oral version of fentanyl that is sucked like a lollipop, offers pain relief within 15 minutes.

**Opioids.** These narcotic medications are used to treat mild to severe pain. They are the strongest pain relievers available and include codeine, morphine, hydromorphone, oxycodone, and fentanyl.

**Adjuvant analgesics.** These drugs were originally approved for the treatment of another illness but have been found to help relieve cancer pain in some situations.



**Q. How do NSAIDs help relieve pain?**

**A.** NSAIDs are taken by more than 30 million people around the world. Prescription and nonprescription NSAIDs—which include ibuprofen (Advil, Motrin), naproxen (Aleve), and ketoprofen (Orudis KT)—are used for any number of aches and pains, including cancer pain. These drugs are effective at blocking chemicals that contribute to inflammation, but they can cause stomach ulcers and serious gastrointestinal bleeding when the drugs are taken regularly and at high doses.

People don't generally tolerate these conventional NSAIDs well when they take them long term. Due to the widespread use of these drugs, researchers are now looking very closely at them and examining, for example, their impact on heart attack. A study published recently in the *British Medical Journal*, analyzing data from more than 95,000 people living in England, Wales, and Scotland, reported that those people who suffered heart attacks were more likely to have been using NSAIDs at the time.

If your doctor has recommended that you take an NSAID for your cancer pain, take it when needed and as it is prescribed. Do not increase dosages on your own. If in doubt, or if the drug doesn't seem to be working as well as you'd hoped, speak with your doctor.

**Q. What is the impact of NSAIDs on the gastrointestinal tract?**

**A.** Stomach bleeding is a well-known side effect of NSAIDs. All of the currently available NSAIDs have roughly equivalent pain-relieving effects, and all can cause some degree of stomach damage. In its early stages, this problem is undetectable, but the onset of a major stomach bleed can be sudden, requiring transfusions and surgery.

Gastrointestinal risk can be significantly reduced when using NSAIDs by taking a class of drug called a "proton pump inhibitor" to help reduce acid production. These include lansoprazole (Prevacid), omeprazole (Prilosec), rabeprazole sodium (Aciphex), esomeprazole (Nexium), and pantoprazole sodium (Protonix).

PPIs target the "proton pump," the multiple pumps in the stomach lining that produce acid. PPIs deactivate some of these pumps, thereby reducing stomach acid production and limiting the chances of ulceration or irritation of the stomach. PPIs may also reduce dyspeptic symptoms such as belching and burning.

**Q. What role does Celebrex have in pain management?**

**A.** For many patients with advanced cancer, COX-2 inhibitors played an important role in pain relief. COX-2 is the umbrella name for the newer and extremely popular cyclooxygenase-2 (COX-2) inhibitors, which included Bextra (valdecoxib), Celebrex (celecoxib), and Vioxx



(rofecoxib). COX-2 inhibitors, ushered in more than five years ago with the introduction of Vioxx, earned a national following thanks to an aggressive advertising campaign directed at consumers.

Used instead of ibuprofen and naproxen, COX-2 inhibitors—the so-called “super aspirins”—were demonstrated in clinical trials to provide pain relief similar to that of other NSAIDs but with a lower risk of gastrointestinal side effects such as stomach ulcers and bleeding from these ulcers.

COX-2 inhibitors are a subset of NSAIDs. As the name suggests, the COX-2 drugs block cyclooxygenase-2, an enzyme linked to inflammation and pain. Traditional NSAIDs, such as ibuprofen and naproxen, block the COX-1 enzyme along with COX-2. Unfortunately, inhibiting the COX-1 enzyme also blocks chemicals that protect the delicate stomach lining and that permit blood to clot. As a result, traditional NSAIDs sometimes cause serious stomach upset or bleeding.

The possibility that these drugs could be associated with serious cardiac side effects was raised in a clinical trial of Vioxx in 2000. However, it wasn't until late 2004 that these concerns became widely publicized and Vioxx and Bextra were removed from the market. Many of my patients at the Cancer Pain Service who were taking COX-2 drugs suddenly became concerned about the long-term safety of this class of drugs, and many panicked, thinking that their primary pain reliever might disappear from the market—or that it might kill them.

As we explained to our patients, every drug has benefits and risks that must be weighed for each individual. The COX-2s, for example, could be extremely valuable for many of my patients for whom conventional NSAIDs had stopped working, or had never worked at all. The drugs could also be valuable for people with gastrointestinal problems who would be at risk of ulcers and internal bleeding if they continued to take traditional NSAIDs.

The percentage of people who may develop heart attacks or strokes because of COX-2 use is very small. Nonetheless, it is important for physicians not to prescribe such a drug indiscriminately, but to reserve it for patients where the benefits will outweigh any possible risk.

**Q. Why are opioid medications considered best for patients suffering the pain associated with advanced prostate cancer?**

**A.** Opioids are prescription narcotic drugs, and their use is backed by detailed research and much clinical experience.

Unfortunately, opioids also conjure up negative reactions. Many patients think the drugs will turn them into addicts, or that the possible side effects (including fatigue and constipation) are unmanageable. Many physicians feel the same way.



However, with proper education of healthcare professionals and patients, opioids can be prescribed very safely for pain management. There are good reasons why these drugs are the mainstay of cancer pain treatment: They are highly effective, and they have few side effects. Moreover, there is no maximum dose as there is with many medications.

Opioids that are used to relieve mild to moderate pain (4 to 6 on the pain scale) are considered weak opioids. These drugs—hydrocodone and codeine—are often used along with other medicines, such as aspirin or acetaminophen, to provide pain relief.

Strong opioids are reserved for severe pain (7 or greater on the pain scale). The drug of choice is morphine. Other popular drugs include fentanyl, hydromorphone, levorphanol, methadone, and oxycodone.

**Q. Why is morphine considered the best drug for severe pain caused by prostate cancer?**

**A.** Even though morphine was derived from opium 200 years ago, pharmacologists still have not found anything better for the relief of severe pain. Morphine can be given in a number of ways, including:

- A short-acting liquid or tablet that is taken every 2 to 4 hours
- A 12- to 24-hour slow-release tablet or capsule that is taken twice daily
- A 24-hour time release tablet or capsule
- A liquid that can be injected into a vein or through a drip
- A liquid that can be given under the skin with a small needle

Most patients starting with morphine are given a short-acting type, which is taken at least every four hours. This way, dosages can be easily and quickly adjusted. Once the patient knows how much morphine is needed to control the pain, the doctor will usually prescribe slow-release tablets containing enough morphine to control pain for 12 hours. These sustained-release tablets are taken twice daily, offering better pain control and convenience. A big plus is that you don't have to remember to take a pill every four hours.

**Q. Do patients develop a tolerance to opioids?**

**A.** People who take opioids for extended periods may eventually have to take higher dosages of the drug to get adequate pain relief. This is because the body becomes tolerant of the drug and the medication loses its impact. In other cases, the pain has increased because of the progression of the cancer, and a higher dosage is needed for adequate pain relief. At this point, the physician may make a small increase in the dosage or prescribe a different type of medication.



**Q. Do cancer patients often become drug addicts after chronic use of opioids?**

**A.** This occurs only very rarely. It's yet another unfortunate myth that has scared many patients away from effective pain medication. It has also led to undertreatment by doctors who mistakenly believe that a patient will become hopelessly addicted to the drug.

Drug addiction means taking a drug to get a psychological "high," not relief from cancer pain. Severe pain requires strong medicine and that is what opioids offer. Studies have reported that only about 1 in 3,000 patients are at any risk of becoming addicted to an opioid after taking the drug for more than 10 days.

**Q. How are opioid medications stopped without causing side effects?**

**A.** If a patient needs to be switched from chronic use of opioid medication to a different type of drug, he is slowly weaned off the opioid over a period of days to prevent any side effects. Suddenly stopping opioids completely can lead to diarrhea, excessive sweating, and a flu-like illness.

**Q. What are the side effects of pain medications?**

**A.** Many patients have heard horror stories of how people who use pain medications become groggy and drift in and out of consciousness, or that they develop terrible constipation that becomes a painful syndrome of its own.

The side effects of opioid medication are easily managed. Granted, patients will become drowsy when they start using opioids and some may feel sick to their stomach. When properly managed, however, these symptoms typically disappear within a week. Drowsiness is reduced by starting medication at low doses and titrating up (gradually increasing the dosage) to achieve maximum pain relief. A number of different drugs can be taken to control nausea.

**Q. Is constipation a common side effect of opioid drug use?**

**A.** Constipation is a common side effect of morphine usage and is very distressing because it can cause even more pain. For this reason, we are as aggressive with a bowel regimen as we are with pain management. Constipation, the infrequent and difficult passage of stool, can begin several days after starting opioid medication, and it should be prevented to spare the patient complications, such as hemorrhoids caused by extreme straining or fissures caused by the hard stool stretching the sphincters. Either of these conditions can cause bleeding, which appears as bright red streaks on the surface of the stool. Fissures may be quite painful and can aggravate the constipation that originally caused them. Fecal impactions may also occur, sometimes accompanied by a loss of control of stool, with liquid stool flowing around the hard impaction.



Constipation can be prevented by gradually increasing your dietary fiber intake. Fiber is roughage—the indigestible parts of whole grains, legumes, vegetables, and fruits. Once it arrives in the colon, fiber absorbs water to create soft, bulky stools, which in turn stimulate a smoother passage into the rectum.

The average American diet is woefully lacking in fiber. Americans typically consume barely 12 grams daily, well short of the recommended 15 to 35 grams. To prevent or eliminate constipation, gradually add more fruits, vegetables, legumes, and unprocessed whole grains to your daily diet.

This upping of fiber intake has to be gradual because a sudden increase in dietary fiber can lead to excessive gas and bloating. Also, drink plenty of water—at least eight 8-ounce glasses daily—to supply the moisture needed to soften the stools.

Regular daily exercise plays a vital role in promoting good bowel function by strengthening the muscles of the lower abdomen and pelvic floor. Walk as little as 20 minutes a day, and you will help to condition those muscles and speed the passage of food through the lower digestive tract.

At Johns Hopkins, patients on an opiate regimen also follow a scheduled laxative program. We have patients using senna, a powerful herbal stimulant laxative, to keep the bowels moving. We also commonly recommend Colace (docusate sodium), a drug that belongs to the family of laxatives known as stool softeners. This medication works by allowing liquids to mix with hard stools. The drug doesn't cause bowel movements, but allows for passage of the stool without straining.

**Q. What is the role for adjuvant analgesics in relieving pain in men with advanced prostate cancer?**

**A.** Adjuvant pain medications (sometimes called co-analgesics) are medications originally approved for another purpose that were later found to help relieve pain in patients with advanced prostate cancer. These drugs include the following:

**Antidepressants.** When used alone or in combination with opioids, antidepressants help relieve nerve pain that does not respond well to other painkillers. An added benefit is that they can improve sleep and help with the depression that often accompanies long-term chronic pain. Interestingly, some of the older tricyclic antidepressants, such as Elavil and Endep, target burning nerve pain particularly well. On the other hand, the newer selective serotonin reuptake inhibitors (SSRIs) such as Zoloft and Prozac don't offer this type of pain relief.

**Anticonvulsants.** These drugs are normally used to control seizures, but they can also help relieve the burning or tingling pain that many men develop with metastatic prostate cancer. The drugs can be used by themselves or taken along with a tricyclic antidepressant. The pop-



ular anticonvulsants include Neurontin (gabapentin), Depakote (valproic acid), and Klonopin (clonazepam).

**Steroids.** Corticosteroids can help relieve bone pain by reducing pressure on the nerves, especially when the pain is caused by suspected spinal cord compression. Cortan (prednisone) or Decadron (dexamethasone) are the popular corticosteroids used for this purpose. A bonus is that the drugs may also relieve the hot flashes in patients undergoing androgen deprivation therapy.

**Local anesthetics.** Lidocaine and other local anesthetics are useful for relieving tingling and burning-type pain. The drugs can be injected into the spine (an “epidural”) or applied directly to the skin to relieve pain or itching.

**Bisphosphonates.** Bone pain and fractures are often a problem in advanced prostate cancer because the proliferation of the cancer cells has damaged bone tissue. Bisphosphonates (such as Fosamax) are drugs that slow the bone damage caused by the cancer. They may also help to control bone pain, reducing the amount of painkillers that must be taken.

**Q. When is palliative radiation therapy needed?**

**A.** Palliative care refers to treatment that alleviates pain without eliminating its cause. Radiation therapy is often needed for painful bone metastases, spinal cord fractures, and nerve root compression associated with advanced prostate cancer. When pain is concentrated in one area, localized external-beam radiation can be used to target a painful bone metastasis. As many as 80% of prostate cancer patients will achieve some degree of pain relief several weeks after the treatment, with bone pain completely eliminated in about 30% to 50% of cases. Pain medication does not have to be taken at this time. The average duration of pain relief from spot radiation is estimated to be three months.

When there are multiple pain sites, wide-field (hemibody) radiation therapy may be used. This therapy uses relatively high doses of radiation and reduces pain in about 70% of cases. This therapy is limited by the fact that it causes nausea, vomiting, and diarrhea, and wipes out key blood-forming cells in the bone marrow, which can lead to infection and the need for a blood transfusion.

**Q. What is the best way to deal with pain caused by spinal compression fractures?**

**A.** When a man suffers a compression fracture of his spine caused by excessive tumor damage, we often look to our radiation colleagues for help. They may recommend a newer procedure called vertebroplasty to restore height in the spine, which will alleviate overall spinal pain. Vertebroplasty is an image-guided, minimally invasive, nonsurgical therapy used to strengthen a broken vertebra (spinal bone) that has been weakened by cancer. Vertebroplasty can help eliminate pain, thereby increasing the patient’s overall function. In



many cases, a man is able to return to his previous level of activity without fear of vertebral collapse. The procedure, often performed on an outpatient basis, is accomplished by injecting an orthopedic cement mixture through a needle into the fractured bone. Vertebroplasty is highly effective because the cement fills the eroded spaces in bone made porous by cancer, thus strengthening the vertebra. The cement stabilizes the fracture, which many experts believe brings about pain relief. As mobility is regained, the patient may be able to reduce or eliminate all pain medication.

**Q. Do alternative approaches have a role in pain control?**

**A.** We offer our pain patients a multidisciplinary approach. When appropriate, we use TENS (transcutaneous electrical nerve stimulation) to treat certain types of pain. This device sends out small electrical bursts to specified areas of the body.

We also offer acupuncture. Studies have reported that acupuncture is effective in controlling the pain, nausea, and vomiting associated with chemotherapy. Having steel needles inserted into your body isn't for everyone, but this ancient Chinese medicinal practice, which is performed with ultra-thin needles, may hold increasing appeal for many men with prostate cancer. Acupuncture remains a well-established method of treatment in Asian cultures, where it has a long tradition—and proponents argue that it would not have survived if it weren't so effective.

Traditional Chinese medicine attributes acupuncture's healing powers to its restoring a normal balance in vital life forces called qi (pronounced chee). Qi is believed to move through 14 major meridians—invisible energy-carrying channels—throughout the body. The energy flow can be accessed at many points along the meridians. Each meridian is associated with specific organs, and every acupuncture point is considered to have a particular therapeutic effect.

Some Western researchers have suggested that acupuncture works by stimulating pain-blocking neurochemicals—either endorphins (powerful substances produced in the brain that deaden pain and alter mood) or other substances that are generated near the site where the needle is applied. The sterile, stainless steel acupuncture needles are extremely thin—about the thickness of two human hairs—and cause little, if any, discomfort. Most needles are inserted just below the skin's surface, less than a quarter of an inch. Some people describe the sensation as a mild tingling, especially when the needle is twirled. The needles are generally left in place for 15 to 20 minutes.

In the United States, acupuncture can be legally performed in all states. However, some permit only physicians to perform it, while others allow supervised or unsupervised laypersons to practice the technique. Approximately 7,000 nonphysician acupuncturists currently use acupuncture to treat pain, depression, insomnia, and other health problems. Also, an estimated 3,000 medical doctors and osteopaths have studied acupuncture and use it in their medical practice. Before seeking acupuncture for any condition, consult your doctor. Like other forms



## PAIN GLOSSARY

Here you will find the key terms most used by experts in describing pain. By understanding the terminology used for talking about pain, you will be better equipped to discuss your own pain with your doctor or healthcare team.

**Acute pain.** Pain that is experienced immediately when the body is injured.

**Adjuvant analgesics.** Medications that have a purpose other than treatment of pain but help relieve pain in some circumstances. These include antidepressants, anticonvulsants, steroids, and local anesthetics.

**Analgesics.** Medications used to relieve pain.

**Breakthrough pain.** A flare of severe cancer pain that breaks through the medication that is already in use for persistent pain.

**Chronic pain.** Persistent pain ranging from mild to severe that is present every day or nearly every day for more than three months. It is usually treated with long-acting medications that treat the pain continually throughout the day.

**Dose titration.** The adjustment of a medication dose upward or downward.

**End-of-dose failure.** A form of breakthrough pain caused when long-acting medication wears off.

**Epidural.** An injection into the spinal column.

**Incident pain.** A type of breakthrough pain caused by a certain activity.

**Intermittent pain.** Long-term chronic pain that comes and goes. It may occur in waves or patterns and is generally treated with short-acting narcotics.

**Intensity.** How much the pain hurts.

**Long-acting opiates.** Drugs used for pain that persists 12 hours or more each day. Also called controlled-release morphine or a sustained-release opioid.

**Non-opioids.** Pain medications that don't contain an opioid. These include non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen, and acetaminophen (Tylenol).

**Onset of action.** How long it takes a medication to begin working.

**Opioids.** A class of both natural (codeine, morphine) and synthetic (oxycodone, fentanyl) drugs used to treat mild to severe pain. These are the strongest pain relievers available.

**Pain threshold.** The level at which a person becomes bothered by pain.

**Palliative care.** A comprehensive approach to treating serious illness with a focus on keeping dying patients comfortable through pain control while also addressing psychological, spiritual, and social concerns. Also referred to as hospice care or comfort care.

**Patient-controlled analgesia (PCA).** A treatment method in which painkilling drugs are delivered directly into the base of the spine, under the skin of the abdomen, or through an intravenous line. A PCA pump operates continuously; if more medication is needed, the patient simply presses a button on the computerized pump to deliver a preset dose.

**Rescue medicine.** Medication that relieves breakthrough pain or pain that is not relieved by regular pain medication.

**Short-acting opiates.** Drugs taken for flare-ups or breakthrough pain because they are effective in a short period. Also called immediate-release morphine and rapid-onset opioids.

**Spontaneous pain.** A type of breakthrough pain with no apparent cause. Can come on very suddenly, even if the patient is at rest.

**Tolerance.** The acclimation of the body to a drug so that a higher dose is needed, or a different medication must be used, to control pain.



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**ADVANCED PROSTATE CANCER TREATMENTS**

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of complementary medicine, acupuncture should be used only as an adjunct to regular medical treatment, never as a substitute for it.

**Q. What is the best way to find a pain specialist?**

**A.** A national survey conducted recently reported that in the United States, only 5% of patients with chronic pain ever go to a pain specialist. The result is a lack of adequate sustained pain relief for the patient, which leads to unnecessary debilitation and reduced quality of life.

If you have pain caused by advanced prostate cancer, you should expect nothing less than having that pain assessed, treated, and relieved. Pain specialists are experienced in the use of many pain therapies, including drugs and patient-controlled analgesia (PCA)—a pump that dispenses medication at the press of a button.

For those who cannot come to an institution such as Johns Hopkins, other fine medical centers around the country are equipped to help you. To find a pain specialist or pain center in your area, contact the American Pain Foundation at 888-615-PAIN (7246). Their address is American Pain Foundation, 201 North Charles Street, Suite 710, Baltimore, Maryland 21201-4111; [www.painfoundation.org](http://www.painfoundation.org)

**Q. Would it be useful to join a clinical trial for pain relief?**

**A.** If you have cancer-related pain, you may benefit from a diminution of that pain in a clinical trial of a novel pain medication or pain therapy. There are other benefits as well from joining a clinical trial. For more information, see page 6.



## TREATING PROSTATE CANCER AND DEPRESSION

*JOANNA L. FINE, M.A., M.D., is a clinical instructor in the Department of Psychiatry at New York University Medical School. Dr. Fine regularly talks to support groups, instructs internists and urologists and, along with her husband, urologist Andrew McCullough, lectures nationally about the emotional care and treatment of prostate cancer patients.*

*“You have cancer.”*

**T**hose three words trigger an avalanche of confused emotions, and the response often starts with “Why me?” All of a sudden, you’re confronted with your own mortality. The world as you know it has been threatened, and all that has given your life meaning, purpose, and enjoyment is now at risk.

Once the diagnosis is given, a person may experience a range of difficult and troubling responses, including sadness, anger, bitterness, and fright. Stress, too, becomes a part of everyday life, triggered by persistent feelings of grief, fear, and anger. In the course of dealing with his disease, a man with prostate cancer encounters several crisis points. It’s not at all uncommon (and certainly understandable) to experience a high level of anxiety when initiating a new treatment regimen and while waiting for the results. Learning that a therapy has failed and that the cancer has recurred, a man may also struggle with pain, chronic fatigue, and the loss of hope. When end-of-life decisions must be thought through and become all-too-real possibilities, new anxieties are triggered.

With the support of family and friends, most men with prostate cancer will adapt within a few days or weeks to their fears about their future. However, some men sustain high levels of sadness, anxiety, and grief for weeks or months. This is beyond the normal adjustment period and typically means that the man has become clinically depressed. It must be noted that depression is not sadness; it is a biological illness with its own symptoms.

It’s now believed that about one in four cancer patients develop depression at some point during their illness. Left untreated, depression can debilitate a man, diminishing his quality of life; it can even effect his follow-through on cancer treatment recommendations that may change the course of his illness.

It’s too often the case that doctors—even many cancer specialists—view depression in a patient with cancer as a “normal” occurrence. Granted, sadness and feelings of grief are nor-



mal when people experience catastrophic losses, but a major depressive syndrome is always considered a condition requiring aggressive treatment. Depression is not a normal consequence of cancer and should be vigorously treated, in much the same ways as the cancer itself is treated.

It is important to remember that depression is very different from sadness. Depression is a syndrome that represents an array of symptoms, including pervasive sadness, inability to experience pleasure, sleep disturbance, appetite disturbance, fatigue, changes in activity, impaired concentration, feelings of worthlessness and guilt, and preoccupation with thoughts of suicide and death.

Depression occurs at much higher levels among men with prostate cancer compared with the general population, and this makes dealing with cancer even more difficult. The importance of diagnosing depression in its earliest stages has been highlighted in recent years by research showing that untreated depression is associated with impaired quality of life, decreased adherence to treatment, and prolonged hospital stays. Depression has also been linked to shortened lifespan.

Medical treatment is readily available to cancer patients with depression. The good news is that the depression generally responds to treatment, which may consist of psychotherapy alone, or psychotherapy plus a course of antidepressant medication.

**In the following questions and answers, I review the causes, symptoms, diagnosis, and treatment of depression in men with prostate cancer, and offer practical advice for getting the most out of the various treatments now available.**

**Q. What causes depression in men with prostate cancer?**

**A.** The exact causes of depression are unclear. It's believed that certain biochemical imbalances in the brain, possibly stemming from a defect in the communication between neurons (nerve cells) in the brain, ultimately lead to depression. Chemical changes in the brain have been noted in depressed people and researchers believe that these changes produce the symptoms of depression.

The brain is composed of distinct regions—each with particular functions—made up of networks of nerve cells that pass messages back and forth. One region thought to be involved with depression is the limbic system, which is concerned with emotional behavior. An area within this system, called the hypothalamus, regulates the pituitary gland, and may be involved in the hormonal imbalances sometimes associated with depression.

Because the individual nerve cells are separated by synapses (small gaps) at each end, chemicals called neurotransmitters are employed to bridge the synapses and pass along messages from one nerve cell to the next. Of particular concern in depression are the neurotransmit-



ters serotonin, dopamine, and norepinephrine. Imbalances in the amounts of these substances appear to lead to depression.

**Q. How prevalent is depression in men with prostate cancer?**

**A.** In general, it is common for men with prostate cancer to speak about how “sad” they are. Sadness is a normal part of life. However, the occasional sadness everyone feels due to everyday disappointments is very different from the serious illness caused by the brain disorder we call depression.

Cancer is diagnosed in more than one million Americans each year; 186,000 Americans are diagnosed annually with prostate cancer. The discovery of prostate cancer is a catastrophic event: Fears about the future, impending death, pain, and suffering are often present. Sadness and grief are normal reactions to a prostate cancer diagnosis. Men typically react to their cancer by experiencing periods of denial or despair, along with a mixture of symptoms of depressed mood, anxiety, insomnia, and irritability. For the majority of patients, these symptoms last a few days to several weeks after diagnosis, but then adjustment should ensue as they learn—with the help of their family, friends, counselors, and physicians—to cope with prostate cancer.

When the emotional upset of prostate cancer lasts for a long time, or when it interferes with a man’s ability to carry out his daily activities, there is reason for concern. Depression is not caused by cancer. However, there is a strong link.

Depression strikes about 17 million American adults each year, with 15% of chronic cases ending in suicide. It’s estimated that 20 to 25% of cancer patients meet the criteria for major depressive syndrome at some point in their illness. Unfortunately, many people simply don’t know what depression is, or they think that they can overcome it by sheer willpower. They can’t. Left untreated, depression can result in needless pain for the depressed person and his family. Fortunately, depression is highly treatable. When they are diagnosed accurately and early, and treated with a combination of antidepressant medication and non-drug therapies, most men can be helped through their depression. They are then able to refocus their energy on their cancer treatment and quality of life.

**Q. Who is most at risk for depression?**

**A.** Some men with prostate cancer are prime candidates for depression. The more severe the cancer, the higher the level of disability, and the more intense the patient’s pain, the greater the risk that a man will develop depression. Men who have a family history of depression, a personal history of depression, or who have had some family member die from prostate cancer, are more likely to become depressed. Risk for depression also rises when alcoholism is involved.



**Q. Why diagnose and treat depression in men with prostate cancer?**

**A.** Depression is associated with a wide range of emotional suffering, including hopelessness, loss of the capacity for pleasure, and, in some sufferers, suicidal thoughts. For the man with prostate cancer, these depressive symptoms often complicate the suffering related directly to the cancer. In addition, men who are depressed and have cancer often have difficulty appreciating—and acting upon—good medical news.

**Q. Is depression in men with prostate cancer underdiagnosed and undertreated?**

**A.** Yes on both counts. Depression commonly occurs in men with prostate cancer, but even though prostate cancer patients with early-stage disease are not much different from other individuals who need treatment, their depression, unfortunately, is too often underdiagnosed and undertreated by internists and cancer specialists alike.

Many factors appear to contribute to this problem. These include:

- the primary care physician's focus is on the cancer rather than on mood symptoms
- a reluctance to stigmatize prostate cancer patients with a psychiatric diagnosis or to burden them with yet another disease requiring treatment
- lack of familiarity with newer, better-tolerated drugs for treating depression
- fears about side effects or drug interactions during the cancer treatment

There has been a tradition in medicine of misconstruing the dark moods of depression as a normal reaction to a serious situation: "He should be depressed—he has prostate cancer!" This misguided but common notion promotes the underdiagnosis of depression, which leads to undertreatment. It's critical that your doctor differentiate between the normal sadness that comes with a cancer diagnosis and abnormal levels of distress triggered by a medical condition called depression.

**Q. What are the most common symptoms of depression?**

**A.** According to the criteria found in the Diagnostic and Statistical Manual of Mental Disorders, a person is suffering a major depressive episode if he continually exhibits four of the following symptoms for more than two weeks:

- Depressed mood with overwhelming feelings of sadness and grief
- Loss of interest and pleasure in activities formerly enjoyed
- Insomnia, early-morning waking, or oversleeping nearly every day
- Decreased energy; fatigue
- Noticeable changes in appetite and weight (significant loss or gain)
- Feelings of guilt, worthlessness, and helplessness
- Inability to concentrate or think, indecisiveness



- Recurrent thoughts of death and suicide; suicide attempts
- Physical symptoms of restlessness or being slowed down
- Disappointment with self

Episodes of major depression range from mild to severe. In mild cases, the symptoms barely meet the minimum requirement for a diagnosis, and the impairment is usually minor. However, severely affected men have difficulty with almost every activity.

**Q. Does currently available treatment help relieve depressive symptoms?**

**A.** Depression responds well to currently available treatment. In about 80% of cases, proper diagnosis and treatment leads to a complete remission.

The treatment of depression has three goals. In order of importance, they are: to relieve the symptoms of depression (depressed mood, insomnia, inability to concentrate); to return patients to their previous ability to function socially and in the workplace; and to reduce the likelihood of a recurrence.

These treatment goals are accomplished in three stages: acute, continuation, and maintenance. Acute treatment focuses on immediate relief from symptoms and restoration of function. Once symptoms respond to acute treatment, continuation treatment is begun to prevent any relapse. If a patient has no symptoms during four to nine months of treatment after an episode of depression, he is considered recovered. At this point, maintenance treatment is initiated to prevent the occurrence of a new episode; this treatment can last for one year or a lifetime, depending on the individual. Depression recurs in about one-half of cases within two years after stopping treatment. However, the longer a person remains in treatment, the smaller the likelihood of relapse.

**Q. What treatments are available for men with depression?**

**A.** They include antidepressant medication; psychotherapy; other treatments, such as electroconvulsive therapy; or any combination of these. It is important to start treatment as soon as possible, since the depression may become more difficult to treat the longer it goes untreated. Response to any particular therapy varies among patients, so a person who does not improve with the first treatment tried may respond to a different one. Medications are probably the most common form of therapy; any given antidepressant has a 70% chance of working.

**Q. What are the benefits of antidepressant drugs?**

**A.** One major approach to treating depression is the use of antidepressant medications. There are several advantages to treating depression with medication: The drugs are effective against mild, moderate, and severe forms of major depression; patients usually respond more quickly to drugs than to psychotherapy (as much as two weeks sooner); and the drugs are



easy to administer. In addition, the medications are not addictive and, when properly administered, are rarely dangerous.

There are now many antidepressant medications available, but selection of a particular medication depends on your symptoms, current medical problems, and the side effects of a specific drug.

Different drugs work for different people, and it's difficult to predict who will respond well to which drug, or who will experience side effects. When a drug fails to produce results after the first four weeks, a new drug may be tried.

For severe depressive episodes, medications are often the first step because of the relatively quick relief they can bring for troubling symptoms. By themselves, antidepressant drugs usually produce a significant improvement within six to eight weeks. If the depression is responding fully to the medication after this period, treatment may be continued for four to nine months at the same level. For the long term, psychotherapy may be needed to address certain aspects of the illness that the drugs cannot.

Despite their efficacy, antidepressant medications are dramatically underprescribed. One study showed that of those taking antidepressants, 39% were prescribed smaller doses than generally recommended for treatment. Some studies show that as few as 3% of cancer patients are prescribed antidepressants.

**Q. What are the benefits of SSRIs?**

**A.** Some of the drugs most recently approved for the treatment of depression are the SSRIs (selective serotonin reuptake inhibitors), such as Prozac, Zoloft, and Paxil. These medications affect serotonin, one of the main neurotransmitters. Serotonin levels have a significant effect on mood and imbalances are associated with such common disorders as depression, obsessive-compulsive disorder, and obesity. Because serotonin affects the brain's ability to process sensory information, low levels of this neurotransmitter can make it difficult to focus or to think clearly.

What the SSRIs do so well is to interfere with the process by which neurotransmitters are taken back up by the neurons that release them. This increases the available supply of serotonin, thus relieving depression.

**Q. What are the advantages of psychotherapy?**

**A.** Psychotherapy alone helps more than half of mildly to moderately depressed persons. It has fewer side effects than medication and may be more acceptable than medication to some patients. Choosing the type of therapy that is best for an individual depends on the severity of the symptoms and the cost of treatment, among other factors.



Combination therapy—using both medication and psychotherapy—is more effective than either treatment alone for mild to moderate depression. This option may be beneficial if either treatment alone produces only partial results, or if the depression is chronic.

**Q. Where should a depressed man seek help?**

**A.** Prostate cancer patients with depression are often reacting to the burden of their cancer and the effect it has on their lives. The majority of patients with depression are treated by a primary care physician. If the diagnosis is in fact depression, the primary care physician can initiate drug therapy and/or coordinate care from other specialists. Short-term psychotherapy can be very effective in helping men with depression.

Many people are confused about whom to consult for treatment of depression. It's essential for someone who feels depressed to consult a trained health professional, such as a primary care physician, psychiatrist, psychologist, psychiatric social worker, or psychotherapist. Here's a brief overview of these medical specialists:

**Psychiatrists.** These medical doctors have several years of postgraduate training in the diagnosis and treatment of mental or emotional disorders. Psychiatrists can prescribe medications and hospitalize patients, and are often consulted in complex cases.

**Psychologists.** Clinical Psychologists have a doctoral degree (Ph.D. or Psy.D.) in psychology and are trained in counseling, psychotherapy, and psychological testing. Most states in the U.S. require psychologists to have postdoctoral training in a clinical setting in addition to the doctoral degree.

**Psychiatric social workers.** These professionals make up the largest segment of the mental health field. A social worker with a Master's degree (M.S.W.) often has specialized training in counseling.

**Psychotherapists.** These mental health professionals may have a variety of levels and kinds of training. They are not legally required to complete a particular degree or take a licensing exam.

**Q. Where can a man find help in choosing the best treatment for his depression?**

**A.** Choosing the type of therapy that is best for an individual depends on the severity of the symptoms. No matter what type of therapy is selected, finding the right therapist may take some research. Your family doctor will be able to provide valuable recommendations, but there are other resources as well. Local prostate cancer support groups, medical societies, university medical centers, and national mental health organizations may be able to provide assistance.



**Q. What is the role of exercise in the treatment of depression?**

**A.** My one caveat here is that you should talk to your healthcare provider before you do anything. That said, exercise can play an important role in improving mood and self-image in men with prostate cancer. Staying active in the early stages of cancer can help men retain quality of life and retard the loss of strength and endurance that often accompanies the disease and its treatment.

Activity, in moderate doses—going for a daily walk with your partner, for example—seems to enhance energy and reduce tension. Some research suggests that a rush of the hormone norepinephrine—the body’s own mood-elevating compound—following more vigorous physical activity helps the brain deal with stress that often leads to depression.

There is not one “best” activity to perform. My recommendation is to do whatever you like and do it regularly, for a half hour or longer, three or more times a week. Ride a bike, go for a swim, work in your garden, play golf, or go for a run. If nothing really appeals to you, then go for a walk and simply enjoy being out in nature.

**Q. Are prostate cancer support groups valuable for men with depression?**

**A.** Support groups are vital in helping men cope with their depression as well as their cancer diagnosis. Talking to others with similar experiences is invaluable in helping men better understand what they’re going through. Cancer support groups can help improve mood, physical symptoms, overall adjustment, perceived quality of life, and even survival.

If you have cancer or you’re undergoing cancer treatment, there are places in your community that can provide help. To find a prostate cancer support group in your area, contact the American Cancer Society ([www.cancer.org](http://www.cancer.org)) at 1-800-ACS-2345; the National Cancer Institute ([www.cancer.gov](http://www.cancer.gov)) at 1-800-4-CANCER; and The Cancer Care Counseling Line ([www.cancercare.org](http://www.cancercare.org)) at 1-800-813-HOPE.



## THE ANATOMY OF HOPE

**JEROME GROOPMAN, M.D.**, *holds the Dina and Raphael Recanati Chair of Medicine at the Harvard Medical School and is Chief of Experimental Medicine at the Beth Israel Deaconess Medical Center in Boston. He serves on many scientific editorial boards and has published more than 150 scientific articles. He is also a staff writer for The New Yorker. His book, The Anatomy of Hope (Random House), was published in 2003.*

**Pandora, the first mortal woman, received from Zeus a box that she was forbidden to open. The box contained all human blessings and all human curses. Temptation overcame restraint, and Pandora opened it. In a moment, all the curses were released into the world, and all the blessings escaped and were lost—except one: hope. Without hope, mortals could not endure.**

**F**or 19 years, I was in constant, debilitating pain. I once had been a marathon runner, but a sudden, unremitting pain shooting down my leg had led me to seek medical treatment. Subsequent surgery on my back failed miserably and the surgeon said there was no hope for me. So excruciating was the pain that I could not walk four blocks without having to stop. I soon gave up all hope I would ever get better. I lived a limited and often painful life as a result.

Nearly two decades later, I revisited the idea of relief from suffering and sought the advice of a rehabilitation specialist in Boston. The doctor was brash and forceful and said that I had been wrong to buy into the assumptions made by other doctors I had seen. He was “in my face” because he quickly realized I had given up all hope that I would get better.

By telling me that there was a path to a better future, he kindled my hope. He said he would design a program for me that would strengthen my back. There was science to his program and it was real. It was hard-core medicine and I would get better, he told me.

Grasping onto the hope he offered, I tried his arduous rehabilitation plan for a period of months and was eventually made healthier. My life is so much better now. I am able to hike, swim, and ride my bike. Although I will never be able to run a marathon again, my outlook has changed significantly.

**Q.** What is your definition of hope?

**A.** People have been thinking about this for millennia. Everyone uses the word but it is actually very difficult to define. I approach it by first distinguishing optimism from hope. An



optimist says, “Everything is going to turn out fine.” Optimism is an innate character trait. But in fact, things do not always work out fine.

Hope is very different from optimism. Hope is an active process. Hope is a clear-eyed view of the world. Hope has no illusions. Hope sees all of the problems, all of the difficulties that we face, and through those troubles, is able to see a possible realistic path to a better future.

Hope has two parts to it. The first is an informational part. You need to learn everything you can about the situation you are in. You need to seek out accurate information. This gives you the first component of hope. Then you become able to see a clear path to a better future, and you experience the emotional aspect of hope. This consists of the powerful uplifting feeling that occurs when you feel that you have a chance to make it. With this feeling of hope comes a series of neurochemical and biological changes in the body that help bring about a restoration of health.

**Q. Why is the world of medicine coming so late to the notion of hope?**

**A.** I was raised in a medical culture where concepts like hope were “soft,” as opposed to “hard science,” with its emphasis on genetics sequencing, the genome, CT and MRI scans, and new medications. The medical profession has been both enthralled and mesmerized by this truly wonderful science. But it also caused us to forget something central to medicine. Every patient who comes to a doctor comes looking for hope. Over the years, I foolishly ignored how powerful hope was in the patient’s mind.

**Q. Is it the role of the doctor to instill hope in patients who despair because of their medical uncertainty?**

**A.** It is critical for doctors to instill true hope in their patients, not false hope. I have given false hope to patients in the past. My intentions were good, but the outcome was not always so good. When I first began practicing oncology, I had a patient named Frances who had colon cancer. I explained that her cancer would go into remission because of the chemotherapy she was receiving. Francis understood remission to mean cure. This was false hope. When Frances and her daughter finally realized that remission did not mean cure, but was only a temporary stage, they never could trust me again.

Since then, I have found that you need to be honest with people and describe the worst-case scenario, but also let them know that sometimes the tumor does not read the textbook, or that sometimes a new drug arrives that can turn things around for the better. This can make a huge difference in a person’s level of hope.

**Q. Oliver Wendell Holmes, the American physician, poet, and philosopher once wrote “beware how you take away hope from another human being.” Should this be emphasized to all medical school students?**



**A.** Yes. I was never taught how to communicate hope effectively to a patient. A doctor's words have a tremendous impact on a patient. I learned this when I was a patient. Words are like a scalpel, and if the right ones are used at the right time, they can yield amazing benefits. If words are misdirected and sloppy, however, they can do a lot of harm. Therefore, it is very important for doctors to understand the power of their words and how to communicate in such a manner that hope is restored or maintained for their patients.

**Q.** Sometimes people who are extremely ill ignore protestations from their doctors and loved ones that they have already tried everything, and insist on pursuing more therapies in hope of a cure. What should be done in this case?

**A.** In my book, I describe the case of a man I call George, who was an eminent pathologist at Harvard Medical School as well as the world's expert on stomach cancer, a disease, ironically, that he contracted himself. At that time, less than one percent of these patients lived past nine months.

George refused to give up hope, and refused to just go home to die in his own bed, surrounded by family and friends, as had been suggested by his doctor. Instead, he insisted on a full course of "curative" therapy consisting of chemotherapy, radiation, and surgery.

Everything seemed to go wrong as George's body fought the cancer and the therapy. He had a raging fever and severe gastrointestinal side effects from the treatment. Although his doctors felt he was going to subsequently suffer an agonizing death, he eventually survived. More than 15 years later, I told him how amazed I still was at his miraculous recovery.

George said to me that it is up to the individual how far he is willing to go in pursuit of a cure. George taught me that each person has the right to hope, even against the longest of medical odds.

If you are fully informed about the ailment you are confronting—George could hardly have been better informed since he was the world's expert on his own disease—then it is your choice to act in a way that you believe will ultimately help you.

George desperately wanted to live, and, even though he realized the odds were so stacked against him, he had to resist his disease as much as he could. He had to try his best to overcome his cancer. He was extremely fortunate, and he did survive.

Other people in similar circumstances say, "I see everything in front of me, the odds are too long, the therapy will wreck my quality of life, and I therefore choose not to do that." That, too, is a completely legitimate decision, and one that I would fully support if I were their doctor.



**Q. What role can clinical trials play in a person's treatment?**

**A.** I think it is very important for people to know the specific goals of a clinical trial they are considering joining. Do the goals of the trial fit their own goals? Most Phase I clinical trials, for example, are not designed to look for benefit, but rather to test toxicity and side effects of a new drug. A person may say, "I have nothing to lose. I am going to be a guinea pig with the understanding that the way this study is structured is to look at side effects. If there is any benefit, I am fortunate."

Other people will look at the trial and say, "I do not want to take that risk and will look for a Phase II or III trial where there may be clinical benefit from participation."

**Q. What can you recommend to a patient when all medical measures have been exhausted?**

**A.** What I do for people like that who are my patients—what I have learned to do over the years—is shift the focus of hope away from the body and onto the spirit. I had a breast cancer patient, Barbara, who taught me so much. Even though she had exhausted all of her treatment options, she was still hopeful.

Hope is an essential part of life and everyone has the right to hope. It is as vital as the oxygen we breathe. The question becomes, what are we hoping for?

We all want a clinical cure when we are in the midst of serious illness. But we are all mortal and there will come a time for all of us when there is no more legitimate hope for the body. At that point, we should still be hopeful, but what we hope for will fit into the realm of the spiritual.

Barbara did not have any options left for her body, and she knew that she was going to die. Still, she knew that she had options for her soul. She could act in a way that would reconcile the important relationships in her life. She was a very religious woman, so she could try to seek a place where her soul was at peace.

I now ask my patients what they feel they can hope for in the time that may remain. How can they reconcile themselves? How can they find peace with loved ones? This is a significant shift that dying patients can try to make. Some people fight it, others will embrace it.

**Q. What would you recommend to an agnostic in the final stages of metastatic prostate cancer?**

**A.** I do think there is a form of spirituality for agnostics. People who are agnostics, atheists, or uncertain in their faith can still find hope and comfort. One place is in the idea of memory.



These people can review the love they experienced in their life and the impact of their life's work. These will be the legacies that will live on long after they are physically gone. They can find hope in all the good they have accomplished, in what they tried to achieve in raising their children, and in maintaining relationships with friends. Their focus at this time should be that all of their contributions on this earth helped make the world a better place in which to live.

**Q. What if you are being treated by a doctor who says that everything possible has already been done, it has not worked, and you now have three months to live?**

**A.** I have made that mistake more times than I want to count. I have since learned that I am not a presiding judge who hands down a death sentence fixed in days, weeks, or months. There have been too many people who have been told by their doctors that they have three months to live and then go on to live a year, or for many years longer.

Biology is variable. Outcomes are uncertain. You have to understand that medicine is an inexact science. Therefore, I do not think doctors should ever give patients a time frame. Instead, you can say, "You are seriously ill and it is uncertain how long you will live."

It is very important that patients get second opinions. No one of us is infallible. Doctors can miss something. I cannot always think of everything and I can fail to suggest a treatment that might be effective.

**Q. What is the role of prostate cancer support groups?**

**A.** Support groups can be extremely important in terms of information sharing. I think they can be important in terms of mitigating the sort of isolation that many sick people feel. They can help diffuse a sense of shame men might feel when their bodies are altered by hormonal therapy, or if they become incontinent or have ED. Support groups can also help restore a sense of identity, worth, and self-esteem for many men.

**Q. How do you help a cancer patient who is without hope?**

**A.** I have learned that it starts by finding out all you can about the patient. You have to know the person's point of reference, his memories, and past experiences. Unless I really partner with that patient and know who he is, I can fall short of finding hope with him.

I once had a patient, Dan, with a curable form of lymphoma. Dan was a Vietnam vet, and I tried to bolster his spirits with military metaphors, such as "We are in the trenches together" and "We are going to blast this cancer." What I did not know was that Dan's best friend from his Army days had died of a different type of cancer. Dan thought he was destined to the same fate and was therefore without hope, no matter what I could tell him.



Here is what helped eventually restored his hope. One day, as Dan was going through his chemotherapy, the nurse placed him next to a woman who had the same type of cancer, who was undergoing the same treatment, and was now on her way to being cured. The two immediately got to talking as they sat there. What this nurse did so brilliantly was to show Dan that, yes, there are walking, breathing human beings who can make it, who have made it, who have survived this cancer. There was real reason for hope.

**Q. In the limited time doctors have to meet with patients, is it possible to instill this type of hope in all of their patients?**

**A.** It is very hard; doctors are enormously pressured, but we should still try our best. We should look to nurses whenever we can, particularly oncology nurses. They are the saints of the saints. They are the ones at the bedside, in the clinic administering the medications, and taking care of side effects. It is the nurses who are often with the patients and they can do so much in terms of helping their patients find hope.

**Q. If a person with prostate cancer is clinically depressed, are they able to have hope that they can recover from their cancer?**

**A.** The chemistry in the minds of these patients is such that they need to be lifted up to a level where they can find hope. True depression is a chemical disorder of the brain, and when you are truly depressed, your brain chemistry will not allow you to hope. I do think you need antidepressant medicine to get you on a level playing field, so you can seek hope.

**Q. An Australian study of lung cancer patients published in the medical journal *Cancer*, a publication of the American Cancer Society, found no correlation between optimism and the ultimate survival in the patients. What did you think of the study?**

**A.** The average survival rate for lung cancer at five years is less than 15 percent. Researchers at a cancer center in Melbourne and other Australian hospitals studied almost 150 lung cancer patients. The scientists found that the patients' level of optimism had no effect on their disease status or ultimate longevity after they had their cancer treatment.

The good part about this study is that the researchers were trying to ask important questions. They are also addressing many unsubstantiated issues that exist in the popular mind, including the notion that if you are not optimistic about getting better, then it is your fault when you do not. The negative side of the study is that optimism is not hope. There is an important difference between the two, as I have already explained.

I have other problems with this study. It is not clear to me whether the researchers studied sufficient numbers of people. They criticize themselves for raising expectations of patients at the beginning of the study to expect a more dramatic effect from the treatment. And they studied only lung cancer patients. Is what they uncovered about optimism also true for



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breast cancer? Is it true for lymphoma?

Two other very important issues, from my point of view, relate to hope. A person's educational level and how they go about assimilating medical information and then making choices, was not studied. It appears that the people in the study did not choose their own cancer therapy. You must remember that one of the greatest things about hope, in terms of potentially influencing medical outcome, is that it allows you to make clear-eyed decisions.

A person with true hope will still have fears and will run through the gamut of emotions. This person also understands that things may not work out for the best, but has the courage and the resilience to try to move forward through all of the difficulties. That's the way real life works.



## ON END-OF-LIFE DECISIONS

**VIRGINIA MORRIS** *an award-winning journalist who researches and writes about health care, medical research, and related social and political issues, is the author of Talking About Death (Algonquin Books of Chapel Hill, 2004). Her book, How to Care for Aging Parents (Workman Publishing Company, 2004), won the Books for a Better Life Award and has been the best-selling book on the topic since its original publication in 1986.*

**L**et me start by reassuring you, lest you have any misgivings. It's okay to read these words, to read about this subject. Reading about death doesn't cause death. It doesn't cause illness. It doesn't even cause depression.

In fact, I have found that learning about death, learning how to one day handle it (and we will all one day handle it), does quite the opposite. Learning about death teaches us about life. Once we overcome our initial discomfort with this subject, we realize that we don't have to be so afraid: Death can be peaceful.

Then we have a second realization, a sort of epiphany: We're not there yet. Life ends, but not now, not yet. We still have it, and so we'd better start relishing it. Having learned about death, we stop fearing it so much, but we also begin to live life, to really live it. So, come with me, dear reader, and don't be afraid. It's okay, I promise.

However, before we head down this path, let me tell you how I got onto this subject. Many years ago, my father was diagnosed with late-stage, inoperable prostate cancer. He was told he might have a couple of years to live. More than five years later, the disease got the best of him, and my father lay in his king-size bed at home, surrounded by his wife and five children, dying.

At first we bustled about, rearranging his pillows, bringing him scrambled eggs and soup (neither of which he wanted), opening windows and closing windows, and generally being neurotic because we wanted him to be comfortable and because we didn't know how else to handle the emotions that were churning inside us.

Gradually, we came to realize that his pillows were okay, and that a few sips of cool water with a squeeze of lime were just about all he wanted. And so we lounged about his room, on the bed and on the floor, and we talked and laughed and reminisced. We recalled our summers on Stony Lake, in Canada—the meandering pine-carpeted paths, the sound of the water lapping against the rocks, the loons crying at night, our endless games of Hearts. With our words, we brought my father to the coast of Maine and onto his dear friend's sail-



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boat, to the laughter of our evenings and the daring dips that came with morning. We talked about our family football games on the front lawn, about the way he always made us squeal when he bombed into the swimming pool and then let one foot rise slowly to the surface. As the nights grew late, we watched old TV shows, we sang silly songs he'd taught us as children, and we loved him with all our might.

During those weeks, my father—my brilliant, driven, commanding father—loosed his firm grip on the control panel, and let us care for him. He softened. He became the gentle man who had always been there, hidden beneath the gruffness of everyday life.

As morphine and cancer took over, he gave one last, mumbling list of instructions to his medical residents, then opened his eyes and called my mother to his side. He didn't speak. He didn't need to. Instead, he took her hand in his and locked his eyes on hers, and in that moment, in that final look, he told her of the unfathomable love in his heart, of the years of joy she had given him. And then, on a beautiful day in April, his work complete, my father took one long, last rattling breath, and left us. Forever.

We stroked back a few stray wisps of hair, we wrapped his big, soft hands around ours, and then we whispered in his ear that he could rest now, that he was safe, and that we would never, ever, forget him. We told him how much we loved him. And then we cried.

It was an exhausting time, both physically and emotionally. Nevertheless, we all agreed that it was an experience none of us would have missed for the world. It changed us. It allowed us to say our good-byes and grieve while we could still love and touch and talk. We had the chance to forgive, to apologize, to hold tight, and to let go.

Two things happened to me in the months after my father's death, two things that propelled me onto this path of exploration. The first was the birth of my baby, Jack, named after the grandfather he would never meet. The juxtaposition of these two events left me stunned. People gave me endless guidance and advice about birth, yet they were strangely silent on the subject of death. It was almost as if it wasn't happening, as if perhaps by ignoring it, we could stop it from happening.

Also, during those months, I had to finish a book I was writing on aging parents. The final chapters were on death and grief, and I had to interview dozens of people about their experiences. But I didn't hear stories of love and reminiscing and laughter. What I heard, repeatedly, were stories of pain, remorse, and regrets. What I heard was, "I don't know how it happened like that," and "He would never have wanted it that way," and "I wish I'd known."

It turns out that the vast majority of people in this country die horribly. Despite any living wills or promises made, they die in hospitals, surrounded not by loved ones but by ominous-looking machines and strangers in blue scrubs. They die in pain, afraid, and alone. For the patient, obviously, this agonizing, lonely death is horrendous. But it is equally horrible for



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family members and other loved ones, who are left with lasting regrets, haunting memories, and insurmountable grief.

I spent four years interviewing doctors, palliative care experts, patients, and families; walking through intensive care units; and trailing behind hospice workers. And what I learned is this: Doctors make poor guides at the end of life, and the system as a whole is like a giant conveyor belt straight into the intensive care unit. However, most of the blame lies with us—the patients, but particularly the family members and loved ones. We are the ones who ultimately call the shots at the end of life, and we come to this task wholly unprepared.

We think we will know what to do, how to handle this. But standing at the bedside of someone we love, our hearts breaking into a zillion pieces, the decisions are far more complicated than we ever imagined, and the emotions, more acute. We aren't ready for this. We freeze up. Suddenly, no matter what was promised or what was signed, we are not ready to make these decisions, we are not ready to let this person die, we are not ready to let go. So we turn to the doctor and plead, "Do something!" We ask for another treatment, an experimental protocol, another machine, because we aren't ready, not yet.

We can change death. We can make it gentler and, in some cases, even meaningful. However, we have to confront it now, today—before anyone calls 911, goes to the hospital, or faces dire medical decisions.

Of course, each of us should have an advance directives—a living will stating your wishes concerning end-of-life care—and a medical power of attorney (also known as a health care proxy), assigning someone the legal authority to make medical decisions on your behalf.

But this is only a start, a bare minimum. Advance directives alone will not change the way someone dies. We have to talk with our loved ones, in depth and repeatedly, about our fears, our hopes, our beliefs and our needs. The typical instructions given in advance—"Pull the plug when it seems hopeless or futile"—are not enough, not nearly enough.

Finally, we need to learn how death happens in the 21st century, the choices that commonly arise, and the possibilities that exist. We need to accept that death happens and brace ourselves to make some very tough decisions. Finally, we need to understand some of the obstacles that frequently stand in the way of our making the best choices.

**The following are questions that I am often asked about dying and death and my answers to them.**

**Q.** How do you start a conversation about dying and death with your loved ones?

**A.** Bring it up at a time when the house is quiet, when you won't be interrupted, and when those involved are rested and can focus, without getting overly emotional. Know that the



first few attempts might not get you anywhere, and the first conversations might be brief. That's okay. Just raise the subject again, another time.

In most cases, the best opening is sheer honesty: "I have no idea what the future holds, but I want to talk to you about my wishes concerning end-of-life care." Once you have named someone as your health-care, or medical, proxy, you can explain to them that, as your proxy, there are certain things they need to know.

Another way to get into this subject is to discuss the death of someone you know

"I don't understand why his family opted for that radiation when Uncle Bill was dying from metastatic prostate cancer," or something along those lines. Or you might bring it up in reference to an article or book you've read.

People tell me, "Oh my parent would never want to talk about that." Then I go to the parent and he/she says, "Oh my children couldn't handle a conversation like that." Do not assume that the other person can't/won't talk about this. It is clearly something we all think about and worry about. Talking might be difficult at first, but once you open the gate, these conversations should alleviate some of the fear.

### **Q. What should be discussed with your loved ones?**

**A.** The sky's the limit. And that's just the point: There is no limit or boundary.

Talk about what would be intolerable to you and why and what you fear about dying. Discuss deaths that seemed particularly "bad" or "good" in your mind.

Fear or dread is always a good place to start because this is often what blocks the conversation. Get it on the table.

People fear pain, of course—both physical and emotional. They do not want to be a burden to their family. They fear loneliness and isolation. They might be worried about unfinished business, or leaving someone behind. But people also worry about unexpected things—being buried alive, or being maimed, or losing their dignity. Probe and explore. What is frightening about this subject?

Once you've pinpointed any concerns, discuss them. How might pain be alleviated? What worries you about being a burden? You might not want your family to care for you, but in fact, they might want the chance to care for you. Caring for you, at least for a limited time, might be a welcome opportunity, a way to say goodbye and ease the grief. So when does caring for someone you love become a burden? How might their loneliness be eased, or any unfinished business wrapped up?



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You'll also want to talk about what you find comforting. When you've been terribly sick in the past, what eased the pain? What gave you solace? Do you want someone to read from a particular book, or is there some type of music that soothes you? Do you like to be touched and massaged or do you hate it? How should medication be managed to balance pain relief and lucidity? What do you think about hospice care?

Talk about how your beliefs and how they affect your view of dying. Do you anticipate an afterlife? How might your spiritual views hamper or ease the process of dying? These conversation topics can lead you in all sorts of directions. Go there. Explore. Learn. But whatever you do, don't try to cover it all in a single sitting. Talk, bring it up again later, and bring it up again when something comes to mind. The discussion should be ongoing.

This subject should also be revisited when you become ill, or when there is new information regarding your health and treatment. Given all you've talked about before, how does this new situation affect your views?

Get your physician involved and discuss various scenarios for the future. How might an illness like this progress? What options would you have? How might you or your family choose among those options? At what point might someone enlist the help of a hospice program?

**Q. You mention “obstacles.” What sorts of obstacles get in the way of having satisfactory discussions?**

**A.** One common obstacle I call, “Where is ‘There?’” Families talk and people sign advance directives, and everyone thinks they know what's what. But then, when families are asked if they want to stop an aggressive treatment, or if they want to call hospice, they say, “Oh no, we're not there yet.”

We think we will know when it's time to switch to palliative, or comfort, care. We expect to be told that any more efforts would be futile. We say with certainty that we know what to do. The problem is that there is no black-and-white division between living and dying.

Modern medicine has not beaten death, but it has changed it dramatically. Today we face far more complicated decisions than ever before. We are not deciding whether to “pull the plug” when everything is hopeless. No, we are deciding whether to proceed with an operation, dialysis, a transfusion, antibiotics. We are making decisions about feeding tubes and hydration. Things may be bleak, but there is usually one more treatment option, an experimental procedure or machine that will keep this person's lungs pumping and heart beating a bit longer.

*We are not facing obvious choices, but rather odds and possibilities and unknowns. We are not simply deciding if life is viable, but if it is desirable.*



We wait to be “there,” at some magical turning point, and in waiting, we often miss the chance to make this death peaceful. We need to realize that we are “there” as soon as there is a diagnosis. We are “there,” making decisions that will affect the way this person lives, and the way he will die.

When considering treatments, it’s important to think in terms of goals:

- What is the goal of a particular treatment?
- What are you hoping to achieve—more time, more comfort, more mobility?
- What are the side effects?
- What other options exist?
- What happens if you don’t do it?
- How long will you give this treatment before you call it quits?
- How will this treatment affect the patient’s life?

Each treatment decision should be reviewed and assessed. Also, while you hope for the best, you should also plan for the worst. Do not put things off. Do not assume you have time—to talk, to forgive, to love.

**Q. What other obstacles can get in the way of a “good death”?**

**A.** When people face these end-of-life decisions—and the majority of deaths occur after family members have decided to refuse or withdraw treatment—an unexpected emotion crops up that sometimes stops families from making the best decision. They feel that by refusing a treatment (or by requesting adequate pain relief) they have not simply allowed death, but that they have caused it. They feel that are actually murdering the person they love.

We have to understand—and we have to understand it deep in our bones— that death is inevitable, that illness causes death, and that we are simply trying to find the most peaceful way through it.

Families also miss opportunities because they have misconceptions about hospice care. They believe that hospice is simply about giving someone morphine and waiting for them to die. They think that it is about “giving up.” And they think that by choosing hospice, the person will die sooner.

Hospice is a team approach that aims at keeping a dying person as active and comfortable as possible. It is not about giving up; it is about changing goals. And it does not cause death. In fact, there is an awful lot of evidence to show that once people are out of the hospital, free of pain, and surrounded by loved ones, they actually live longer than if they had remained in the hospital.



**Q. How much detail and specificity is required in an advance directive?**

**A.** People have written advance directive forms that include pages and pages of detail. They have made charts that describe a dozen illnesses and then a corresponding list of treatments that would be acceptable and unacceptable in all those various situations.

I don't believe that it is possible to catalogue all the possible end-of-life scenarios, much less to know in advance which treatments you would want in some theoretical and unimaginable situation.

We cannot choreograph our deaths in advance, ticking off a list of instructions for an event that is likely to be far more murky and chaotic than we think. But we should give our loved ones some general instructions, and it is helpful to attach a personal letter reminding them of our views and beliefs, and offering reassurance that they are doing the right thing. A letter like this—your voice whispering in their ears as they face these decisions—can be a source of great comfort to those who must one day read it.

As I mentioned earlier, learning and talking about death is never easy, but it is oddly empowering and life-affirming. Thinking about death and ultimately accepting it as an integral part of life reminds us of what's important. We will always get caught up in the irritations of the day. We will gripe at our spouses, worry about trivial things, and fall into bed feeling lonely and tired and sad. We will feel insecure and wrestle with anger. Life, with all its ups and downs, goes on.

But when we are aware of death, we will have more of the other moments—moments when we realize how short it all is and how much, how very much, it all means. We will have moments when we stop and feel it—the life, the breath, the clarity. We will walk away from the mess, or shrug at the sagging reflection in the mirror, or decide that a project can wait, and look out at the world and think it's grand, quite grand, to be alive for one more day.

Death is sad, but it is not simply a dark hole, an awful pit, into which we fall. Death is also a brilliant light that shines on all the life that comes before, and all those days, those precious days, we still have.

**End-of-Life Aid**

The National Hospice and Palliative Care Organization (NHPCO) is a nonprofit support group, headquartered in Alexandria, Virginia, that provides a toll-free help line (800-658-8898) and a website ([www.caringinfo.com](http://www.caringinfo.com)) offering all the information you might need concerning hospice service and end-of-life care issues. NHPCO offers free brochures on topics including advance care planning, caregiving, hospice and palliative care, grief and loss, and pain. NHPCO also provides free state-specific advance directive documents and instructions.



## GRAND ROUNDS

*Hospitals regularly present Grand Rounds for their physicians. A doctor describes a case history along with clinical presentation and possible treatments. In every issue of the Johns Hopkins Prostate Bulletin, Grand Rounds offers readers a chance to present questions about the prostate, with a Johns Hopkins physician offering responses. The Grand Rounds in this section presents frequently asked questions about what to do when cancer recurs following prostate surgery, brachytherapy, or external beam radiation therapy—and responses from Hopkins prostate cancer experts. (Of course, these responses cannot replace the specific advice of your physician.)*

### Cancer Recurrence Following Surgery

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#### Fear of Recurrence

**Q.** I recently had a radical prostatectomy at age 58. Other than periodic PSA testing, is there any other way to be assured that cancer cells did not previously escape into my bloodstream? Prior to my surgery, my PSA was 14.4 ng/ml and my Gleason score was 6. Cancer was in two lobes and rated a stage T1C. Following surgery, my PSA has been 0.1 ng/ml. My father died of prostate cancer at age 63 and I have two brothers who currently have prostate cancer and are on hormonal therapy. I'm concerned about my outcome and can't get it out of my mind that some cells might have escaped. Are the odds against me? **Jasper, IN**

**A.** After surgery for prostate cancer, if no cancer remains in the body, the PSA should remain below 0.1 to 0.2 ng/ml. If the tumor was organ confined and Gleason score 6, the chance of residual disease is around 8%. The chance of developing a detectable PSA becomes smaller after five years and is around 1 to 3% between five to ten years for those men with organ-confined, Gleason-score 6 disease.

#### Radiation for Recurrent Cancer

**Q.** A PSA test result of 13.4 ng/ml and a Gleason score of 7 prompted me to have my prostate removed three years ago. The surgeon later discovered that the cancer had spread to one seminal vesicle but not the lymph nodes. For a year, PSA tests at three-month intervals yielded readings of 0.0. But more recent tests have revealed steady PSA increases: 0.15, 0.2, and 0.4 ng/ml. My surgeon is recommending radiation treatments. What is the best option? **Bethel, OH**

**A.** When high-grade disease (Gleason score of 7 or more) is present in the seminal vesicles, the disease has most likely spread beyond the area where the operation took place (the prostate bed). Radiation therapy would be unlikely to result in a durable suppression of the PSA (i.e., eradication of all cancer). There are other possible approaches. One



approach is to withhold therapy and follow up with PSA tests and yearly bone scans. This would maintain the current quality of life.

A second approach is to initiate androgen ablation therapy (hormonal therapy) to suppress PSA. This would, however, result in reduced quality of life without strong evidence that length of life would be increased. A third approach is to become involved in experimental protocols, usually under the direction of a medical oncologist in a university setting (e.g., dietary manipulation or use of drugs thought to delay progression).

### Chemical vs. Surgical Castration

**Q.** I'm 82 and was recently found to have a Gleason score of 8. My doctor immediately started me on hormone therapy. Since sex is no longer an issue for me, what do you see as the pros and cons of surgical versus chemical castration? **Ormond Beach, FL**

**A.** There is no difference between the two forms of castration in terms of delaying progression of prostate cancer. However, chemical castration is more expensive (\$5,000 per year) when compared to surgical castration (\$2,000 one-time cost) and requires compliance in terms of remembering to schedule the injections. With surgical castration there is no concern about testosterone levels remaining low; whereas non-compliance with chemical treatment could result in the return of testosterone levels to normal. The advantage of chemical castration is the absence of any psychological effect from removal of the testicles.

### Possible PSA Rise

**Q.** I had a radical prostatectomy performed 18 months ago, when I was 63 years old. My PSA was 5.0 ng/ml and my Gleason 3 + 3 = 6. The surgeon told me that everything went as well as could be expected. There were no positive margins and nothing found in the lymph nodes.

Four months after the surgery, my PSA was .002 ng/ml and eight months later it had moved to .006 ng/ml. Three months ago, my PSA was 0.1 ng/ml and I became concerned. My next scheduled test is in three months. My urologist has told me that if the PSA is higher than 0.1 ng/ml, he wants me to consider both radiation and hormonal treatment. I am at my wits' end, in light of the fact that my surgeon had told me that everything had gone so well. Your counsel would be helpful. **Grand Rapids, MI**

**A.** Cancer can recur even if the pathology report from the initial operation is favorable. However, it appears that many recurrences are slow, and in some of these cases, treatment need not be started right away. In a selected group of patients whose cancer returned after radical prostatectomy, we found that approximately one third had a more aggressive pattern of recurrence. In general, these patients had either Gleason 7 disease at the time of surgery, signs of seminal vesicle invasion, or lymph node invasion. This group generally had PSA val-



ues that doubled every ten months, and many of them progressed to metastatic disease. The other group had longer doubling times for their PSAs. Many have been followed for years with little sign of clinical disease or tumor recurrence.

The benefits of early hormonal therapy in delaying progression of disease are questionable. Only one study has ever shown that early administration of hormonal therapy can prolong life in patients whose tumors continue to grow. Hormonal therapy has side effects including hot flashes, erectile dysfunction, loss of libido, weight gain, and bone demineralization. For this reason, with the exception of pre-treatment for definitive radiation therapy, we usually reserve hormonal therapy for patients who have clinical signs of advanced disease.

Additional radiation therapy for early recurrence after surgery remains a controversial subject. In our experience, 85% of patients whose cancer recurs will have metastatic disease with or without a local recurrence. It is questionable whether additional radiation therapy will help them. Indeed, in the majority of patients undergoing post-surgical radiation therapy, the PSA will fall for an average of only two years before beginning to rise again.

When there is likely evidence of local recurrence on physical examination, or if the recurrence comes many years after surgery, additional radiation may be warranted. If the PSA rises soon after surgery in the setting of negative surgical margins, a distant recurrence is more likely. In that situation, we let the doubling time of the PSA determine how aggressively to treat the patient.

### Radiation Following Surgery

**Q.** My husband had his prostate removed last June. His recent PSA test was 2.8 ng/ml and last week the doctor called and said my husband needed radiation therapy immediately. My husband is 52 years young, tends to go by what his doctors tell him, and doesn't ask any questions. I'm the opposite and I'm not so sure we should rush into this without getting some more information. Any information would be appreciated. **Santa Fe, NM**

**A.** It is known that radiation therapy is not likely to be beneficial in men after radical prostatectomy for prostate cancer if the PSA does not become undetectable, or it begins to rise in the first year after therapy. This is because these men almost always have disease that is beyond the area (pelvis) where radiation therapy will be directed. No test available today can reliably identify microscopic cancer cells beyond the pelvis.

### When Hormonal Therapy No Longer Works

**Q.** My father is 68 years old, never smoked, and has excellent cardiovascular function. Unfortunately, I can't say as much for his prostate. Seven years ago he was diagnosed with prostate cancer after his PSA reached 2,500 ng/ml. He had metastatic lesions throughout his body and an orchiectomy was performed. With Lupron and Zoladex no longer effective,



what can be done about his PSA, or doesn't that matter anymore in such an advanced case? What do you recommend? **Sag Harbor, NY**

**A.** Withdrawal of androgens by removing the testicles (orchiectomy) or using medications (Lupron/Zoladex) is the first-line therapy for advanced prostate cancer. When a patient no longer responds to this first-line therapy, an oncologist will often recommend the addition of an antiandrogen or other hormonal approaches (second-line hormonal therapy) to see if the PSA will respond. When hormonal therapy is no longer effective and the disease is progressing, chemotherapy is then used to delay its progression.

#### **Orchiectomy Or Hormonal Therapy?**

**Q.** I am 79 years old and have been physically active my entire life. My father died of prostate cancer at 74, so I have always been aware of a possible susceptibility. When I was 68, I was found to have a high PSA and my prostate was removed. Periodic PSA exams over the years showed a little movement but nine years ago, it reached 3.2 ng/ml and I started hormonal therapy with injections (Lupron) and pills (Casodex) to lower my PSA. My PSA has been undetectable since then. Although my medication is still covered by my insurance policy, I was wondering whether it would make any difference in my prognosis if I had an orchiectomy and didn't have to take the Lupron any more? **Tallahassee, FL**

**A.** The goal of hormonal therapy (medical castration) and orchiectomy (surgical castration) is to lower testosterone to "castrate" levels (levels that would be present after removal of the testicles). Some men who have been on hormonal therapy for prolonged periods (years) will maintain castrate testosterone levels when hormonal therapy is discontinued because the signal for testosterone production has been permanently suppressed. Therefore, in men who have been on hormonal therapy for many years and want to discontinue it, an alternative to surgical castration is to discontinue the hormonal therapy and monitor the testosterone level to see if it remains low.

#### **Multiple Therapy Approach**

**Q.** Why is the war on prostate cancer not being fought on all fronts at the same time? By this I mean, why not use radiation, hormones, cryotherapy, and a radical prostatectomy when fighting the insidious cancer? Prostate cancer has a recurrence rate that leaves me doubtful that only one approach can get the job done, which means a cure. What are your thoughts, please? **Grand Gorge, NY**

**A.** The problem with using multiple approaches that target only the prostate and surrounding tissue (surgery, cryosurgery, radiation) is that failure to cure is most often the result of the presence of microscopic foci of cancer far beyond the reach of the prostate (i.e. lymph nodes/bones), despite the fact that it is not seen using any tests we have available today.



Therefore, treatment that simply targets the prostate area (no matter how effective) will not totally eradicate disease that is distant. Hormonal therapy can slow the progression of distant disease but is not curative. Therefore, what we really need is an effective treatment that targets distant disease, not combinations of treatments that are directed only at the prostate.

## Cancer Recurrence Following Brachytherapy

### Rising PSA After Brachytherapy

**Q.** Is there any reason to be concerned about the 89 palladium seeds implanted in my prostate several years ago as the principal treatment for my prostate cancer? I am 81 years old. I am checked semi-annually. My PSA continues within normal ranges but is slowly rising. **Belleair Beach, FL**

**A.** Prostate cancer is a disease with a long natural history, meaning that it takes longer than a decade for an early localized prostate cancer to progress and cause death. Many men diagnosed with prostate cancer and treated at an older age—even if not cured—will have no adverse effects from the disease while they live out the remaining years of life. The chance of death from prostate cancer, of course, depends upon the extent and aggressiveness of the disease at diagnosis, and how much remaining time is left for progression (life expectancy). That said, an 81-year-old man with a slowly rising PSA is much more likely to die of a cause other than prostate cancer during the remaining years of life.

### Hot Flashes

**Q.** I am 72 years old. Five years ago, I underwent brachytherapy for my prostate cancer. My PSA at the time was just over 15 ng/ml, but dropped steadily to 0.8 ng/ml. It remained undetectable until 15 months ago, when it started to rise rapidly. My PSA was 10 ng/ml and I started using Casodex, with no untoward side effects other than an increase in breast size. The strange thing is that I have recently begun to experience transient hot flashes. Why has it taken so long for these side effects to begin and when, if ever, will they disappear? **Orlando, FL**

**A.** Approximately 13% of patients on Casodex have hot flashes (also called flushes) due to the release of opioids in the hypothalamus—an area of the brain involved in temperature regulation. It is not clear why some men develop symptoms and others do not, or why symptoms may be delayed in some men. Hot flash symptoms can be alleviated by treatment with low-dose estrogens or progesterones.



### Treating Recurrent Cancer Following Brachytherapy

**Q.** I had seed implants shortly after my cancer was diagnosed. I was 58 at the time. My cancer came back ten years later, and I was told that I had five years to live. My new doctor now tells me I have an extra year. I am taking Casodex and wonder if this will help me at all at this point? I have arthritis in my back and I'm not sure if I'll be able to differentiate the pain of arthritis from bone cancer. What do you think? **W.R., Mill Creek, WA**

**A.** The treatment for progressive prostate cancer after an attempt to cure the disease with local therapy (seed implants) will eventually involve androgen ablation or withdrawal of androgens (hormonal therapy) usually by medicine (medical castration). The timing of hormonal therapy is controversial. Some physicians recommend starting treatment early (when the PSA becomes detectable), and others recommend starting the treatment later (when there are symptoms or evidence of disease radiographically). The source of 95% of androgens is the testicles. Removal of the testicles (surgical castration) or the use of drugs (LHRH agonists like Lupron and Zoladex) that interfere with a signal from the brain to the testicles (medical castration) results in removal of most androgens (95%).

The adrenals are the source of a smaller amount of androgens that probably play little, if any, role in progression of prostate cancer after removal of the testicular source of androgens. However, some physicians use antiandrogens like Casodex (a drug that blocks adrenal androgens by interfering with the androgen receptor), believing that they will delay progression of disease and prolong life when combined with testicular androgen ablation. The combination of an LHRH agonists (androgen ablation) and an anti-androgen (blockade of adrenal androgens) has been termed total androgen ablation.

Although there is no strong data to support the use of total androgen ablation, it is standard practice to add an antiandrogen when there is disease progression (usually rising PSA) on an LHRH agonist. This may decrease PSA in some men but is usually short-lived.

When the PSA begins to rise in the setting of total androgen blockade, some men will have a further PSA decrease with withdrawal of the antiandrogen. This is because of an alteration in the cancer cell that allows the antiandrogen to act as a hormonal stimulus rather than a block. Therefore, it is also standard practice to withdraw the antiandrogen in the setting of PSA progression if total androgen blockade is being used.

Distinguishing between the pain from arthritis and bone metastases from prostate cancer could be difficult, but a comparison of old and new bone scans will usually help clarify the issue. If there is confusion, MRI is an excellent method for further defining bone lesions from cancer.



### Thoughts On Brachytherapy

**Q.** I'm 62 years old and in good health. In June 2000, I was diagnosed with prostate cancer. I had an enlarged prostate and had been taking Flomax for the BPH. In September 2000 I had a TUIP procedure (transurethral incision of the prostate) followed three months later by brachytherapy for my prostate cancer. Over 100 radioactive seeds were implanted in my prostate. I'm now concerned about the future. What options are open for me if 1) I develop any problems urinating or 2) if my cancer comes back? **Tiverton, RI**

**A.** One of the problems with brachytherapy in men with BPH is that if they develop bothersome lower urinary tract symptoms not relieved by medication after brachytherapy, surgery for BPH (TURP) is associated with a very high rate of incontinence. When there is residual cancer detected after brachytherapy, the choices for treatment would depend on the grade and extent of the cancer at the time of detection. Radical prostatectomy after brachytherapy is rarely performed because of the higher risk of incontinence and rectal injury.

### Close Observation After Cancer Recurrence

**Q.** I'm 89 years old. Last year, I had a seed implant and everything was fine until recently, when I got a PSA reading of 7.1 ng/ml. The surgeon who did the implant suggested I speak with my urologist about further treatment since "we did not kill all the cancer." I am worried and would like your advice about what to do. **Long Island City, NY**

**A.** At your age, observation would be a rational approach to prostate cancer that is not totally eradicated by treatment directed at the prostate (surgery/radiotherapy). If there is no evidence of metastatic disease in bone, most men will remain asymptomatic for many years before further treatment with hormonal therapy is necessary.

## Cancer Recurrence Following External Beam Radiation Therapy

### Recurrent Prostate Cancer

**Q.** I was diagnosed with prostate cancer 11 years ago, when I was 74. I had radiation therapy and followed up with regular visits to my urologist every six months. My PSA has remained in the 1.1 ng/ml–2.2-ng/ml range. My urologist recently performed a biopsy and when the results came back, I was shocked to receive a diagnosis of ductal adenocarcinoma.

From what my doctor tells me, this is a rare prostatic malignancy previously known as endometrial carcinoma of the prostate. He said it usually has an aggressive behavior. My



latest PSA is 1.1 ng/ml. In your opinion, should I consider starting hormonal therapy? Is IMRT radiation a possibility? Alternatively, due to my advanced age, should I carefully monitor the situation and not undergo any treatment right now? **Via E-mail**

**A.** Ductal adenocarcinoma of the prostate presents in less than 1% of all prostate cancers. When the disease is first discovered, radical prostatectomy is the treatment of choice, although the final pathology report will show advanced extraprostatic disease in almost 70% of cases. If you have already undergone radiation therapy, surgery would not be a safe option for you. Additional radiation therapy is unlikely to be helpful, and IMRT is most likely contra-indicated because of your previous radiation therapy.

Hormonal therapy is not appropriate because ductal adenocarcinoma, unlike the more common acinar (glandular) adenocarcinomas, is hormone insensitive. This tumor may respond to solid tumor chemotherapy agents such as Taxotere. It usually does not produce PSA, which is why your PSA level remains low. This is most likely a new tumor arising from the prostate. You need to speak with an oncologist.

#### **If The Cancer Returns After Radiation**

**Q.** I was diagnosed with prostate cancer six years ago, when I was 57. I had radiation and hormone therapy at my local hospital. After completion of therapy (two months of radiation and three months of hormones), my PSA dropped to .033 ng/ml. It had been a little over 7.0 ng/ml when the treatment began. My Gleason grade was 3+2 on the base of the right lobe, and 3+4 on the right lobe. All other results of the test were negative, including the left lobe.

Over the past six years, I have visited my doctor every six months, although he changed it recently to once a year. My PSA scores (I've been tested every six months) have ranged from a high of .40 ng/ml to a low of .22 ng/ml, with my most current result being .23 ng/ml. I have two questions: Based on this information, what do you feel is the likelihood of the cancer returning? Secondly, if the cancer were to recur, what would be my best options? **Via email**

**A.** Because there is no surgical pathology specimen to review after radiation treatment (as there is after radical prostatectomy), it is much more difficult to issue a prognosis based on original biopsy findings alone.

Radiation therapists define post-radiation recurrence as three successive elevations of PSA in a row. Because all the prostatic tissue remains in the body after radiation therapy, some degree of PSA can still be produced. Unless and until there are three successive elevations, you would be considered free of cancer.

The technical term used in clinical oncology is NED: No Evidence of Disease. If the PSA starts rising, the only remaining standard option is hormonal therapy. When it should be



started remains a matter of intelligent choice for patients and practitioners. There are no standards established for treating post-radiation therapy recurrences.

In patients who have undergone surgery and show a rise of PSA, the rate of PSA doubling has been shown to correlate with the eventual appearance of metastases. The patients who seem to be at the highest risk of developing metastases are those in whom PSA doubles every ten months or less. These patients are more likely than not to need hormonal therapy.

Whether patients with slower PSA doubling should also receive hormonal therapy is not known at this time. Regardless, it is not possible to just transpose these approaches to the radiation therapy population of patients. Standards will have to be worked out for these patients separately.

### Hormonal Therapy After Radiation

**Q.** I am 79 years old and my prostate cancer has come back seven years after my radiation therapy treatment. My doctor recommends hormone therapy, but I have two questions about its application. What are the differences between intermittent and continuous hormonal therapy? Do you prefer one to the other? **Beacon Falls, CT**

**A.** Standard hormonal therapy has been used for advanced prostate cancer for over 50 years. The side effects of hot flushes and weakness, and the long-term possibility of weight gain and bone demineralization, have led to limited enthusiasm for long-term administration of this approach to patients with slow recurrences, and may even make treatment difficult for some patients who need the treatment for aggressive recurrences.

For these reasons, a method of giving an occasional injection of medication to stop hormonal production has been used because the effects on the tumor may last much longer than the side effects from the treatment. The patient is treated until there is a good response in the PSA or other marker of tumor growth, and then the treatment is stopped until the PSA rises again to a pre-determined level, anywhere between 5 to 15 ng/ml.

No standards have been established for this kind of treatment. It does not appear superior or inferior to standard hormonal therapy for controlling cancer growth, and it has not replaced continuous hormonal therapy, which remains the treatment of choice for most patients who need hormonal suppression.

In general, intermittent treatment requires excellent communication between the patient and the medical staff, easy access to treatment and monitoring facilities, and a high level of motivation on the part of both patient and practitioner. Bottom line: Intermittent hormonal therapy is not for everybody.



### Hormone Duration

**Q.** I have been taking Lupron for my recurrent prostate cancer for six months. My PSA has dropped from 22 ng/ml to 3.2 ng/ml, and my doctor believes it may drop further. If it does go down more, and stays at that greatly reduced level, how long can I expect it to remain that way? **Buena Vista, VA**

**A.** For a long time, the average duration of response to hormone therapy was quoted as being around 18 months (frequently quoted average duration ranges are 12 to 33 months). However, today, hormonal therapy is used for so many patients with widely varying stages of the disease that I believe it is too difficult to generalize.

In general, the earlier and less aggressive the disease when first treated, the longer the response. Unfortunately, this is such a generalization that I don't think it's useful for the majority of patients who need an answer to the question that is foremost in their minds: "That's fine for the majority, but what about my case?"

Because of the earlier use of hormonal therapy and the possibility that this treatment may delay the development of metastatic disease, many patients will continue to live for many years even after hormonal-resistant disease begins to emerge. Once again: "That's fine for the majority, but what about my case?" As a rule, the rate at which the PSA doubles remains the best indication of the current trajectory of the disease.

### Rising PSA After Radiation Therapy

**Q.** For a two-month period two years ago I underwent radiation treatment for prostate cancer. Prior to treatment, my PSA was 6.3 ng/ml and I had a Gleason 7 score. During the treatments I began to experience blood in my stool. My PSA dropped to 0.07 ng/ml and remained at this level until a year later, when it rose to 1.3 ng/ml. Two months later, it was 2.5 ng/ml and upon testing again two months later it was 2.4 ng/ml. Are these signs that the cancer has recurred? Also, is the blood in the stool a marker of problems? I am 80 and otherwise in very good health. **New York, NY**

**A.** Blood in the stool after radiation therapy almost always represents radiation proctitis (inflammation of the rectum) and is not a serious life-threatening problem. It can be treated locally with agents that decrease inflammation. However, a rising PSA profile after any form of treatment for prostate cancer—hormonal, surgical, radiotherapy—indicates that the disease has not been completely eradicated.

However, it does not mean that you are in any immediate danger. For example, after radical prostatectomy, when men develop a detectable PSA, an average of eight years elapse before the disease becomes apparent on any radiographic test (e.g., bone scan). After that, the disease can be controlled for an average of three additional years. Thus, an 80-year-old man



with treated prostate cancer has a very high chance of living out his normal life expectancy without harm from prostate cancer.

### Chance Of Cancer Recurring

**Q.** I am 65 years old. I chose radiation beam therapy for my prostate cancer treatment in 2001. My PSA was 9.6 ng/ml and my cancer was classified as Stage 2. Since my treatment, my PSA has gone down every year. Now, four years later, it is 0.95 ng/ml. I am still worried, however, and want to know what the chances are that the cancer will recur. **Kansas City, MO**

**A.** After radiation treatment, the PSA reaches a lowest level (nadir) and stays there as long as the cancer is inactive. Radiation therapists define cancer recurrence as three successive increases in PSA. This is different from recurrence after surgery, which is defined as any PSA level above the post-prostatectomy range. After surgery, the chances of recurrence can best be predicted by the original surgical pathology report, which shows the Gleason score and extent of tumor, giving the patient a pathological TNM stage. The TNM (tumor, node, metastasis) system is used by physicians to describe how far the prostate cancer has spread.

The TNM system assigns a T number (T1 to T4) to a tumor according to its extent on a digital rectal examination (DRE); an N number (N0 to N3) indicating lymph node involvement; and an M number (M0 to M1) to indicate the presence of distant metastases. These stages are further subdivided into a, b, and c to describe how the cancer was diagnosed and the extent of cancerous tissue.

The most commonly diagnosed stage of cancer today is T1c, indicating that the cancer was not found during a digital rectal exam but was identified by needle biopsy performed after finding an elevated PSA.

Radiation therapy has no similar report, so one must rely on the original parameters prior to treatment: PSA, Gleason grade on biopsy, and clinical TNM stage. The lower the original PSA and Gleason score, and the more normal your prostate felt before treatment, the better your long-term outlook.

### Bone Scan

**Q.** I am 77 years old. In March, 1996, my PSA increased to 13 and a later biopsy indicated prostate cancer, with a Gleason score of 7. I now get monthly Lupron injections and take Casodex daily. A bone scan showed some metastatic growth; radiation was not recommended. My PSA has been at 0.1 and my new oncologist recommends that I get a bone scan only if my PSA begins to rise. Do you concur? Also, is it too late to consider radiation therapy? **Little Falls, NJ**



**A.** Although unlikely, it is possible for prostate cancer to progress while PSA remains stable. For this reason, I recommend a yearly bone scan for men who have metastatic prostate cancer and no symptoms even when the PSA is not rising. Radiation therapy directed at the prostate is not recommended in the presence of metastatic disease because it won't eliminate the cells distant from the prostate. In the setting of metastatic disease, radiation therapy (spot radiation) is used to treat painful bone metastases or disease that is causing destruction of the spine and neurological symptoms.

### Slowing The Progression of Cancer

**Q.** My dad (currently 91 years old) was diagnosed with prostate cancer about 20 years ago and started taking Lupron regularly at that time. His cancer had been under good control the entire time. About two months ago his PSA jumped to 26 ng/ml and his urologist recommended skipping his next Lupron injection (scheduled for the next week) and instead ordered a "full body bone scan." The scan showed "wide-spread metastasis." Two weeks later, his PSA was checked and it was 50 ng/ml. At that time he was given a Lupron injection and in two weeks time his PSA jumped again to 90 ng/ml. His urologist referred him to an oncologist and told us that he didn't think my father had more than 24 months to live. My Dad still gets around and takes care of his own needs and his mind is sharper than mine. What should I be looking to do for him now? Is radiation an option with "wide spread metastasis"? **Incline Village, NV**

**A.** When prostate cancer progresses despite hormonal therapy, most oncologists will try second-line hormonal therapy with an antiandrogen like Casodex or Flutamide added to the Lupron injections. When second-line hormonal therapy is no longer effective, chemotherapy can be used to slow the progression of disease. When prostate cancer is metastatic to bone, radiation therapy is only used to treat small areas of localized tumor causing pain or weakening of the bone.

### Metastatic Disease

**Q.** I am 80 and have been in excellent health for most of my life. In November 1996, my PSA was 6.6 ng/ml. It rose to 18 in May, 1997. A biopsy showed a Gleason score of 8. My bone scans and MRI were negative for metastasis. I underwent 3-D conformal radiation along with five months of androgen blockade before, during, and after the procedure. Following radiation and blockade, my PSA dropped to 0.2. However, it rose rapidly to 5.4 in just seven months.

Although asymptomatic, I am back on hormones, and my PSA is currently 0.4. The medical oncologist who advises me says that micrometastatic disease is likely but that no further local treatment would help. He wants me to continue intermittent androgen blockade. My urologist, on the other hand, advises salvage surgery. Since all scans show no evidence of disease, he thinks this may be a cure or, at least, may help to debulk my prostate. My physicians are



in disagreement and I'm confused and undecided. Any suggestions that would help me choose a course of action would be appreciated. **Irvine, CA**

**A.** It has been well documented that early (within the first year) PSA relapse after surgery or radiation therapy is a strong marker of metastatic disease. In the setting of metastatic disease, local therapy is ineffective and unlikely to prolong life. Thus, surgery at this point probably won't be beneficial and it could result in a reduced quality of life. You run a high risk of urinary complications after this surgical procedure, made more difficult by scarring from radiation therapy. Considering the tradeoff, surgery does not seem rational.

#### **Surgery After Radiation Therapy**

**Q.** I am 75 years old. After being diagnosed with cancer (Gleason score of 7), I underwent radiation therapy. My PSA dropped but—after four years—it is on the rise again. My doctor recommends hormone injections, but I am wondering if I might be better off undergoing a radical prostatectomy at this point. I would appreciate your counsel. **Harper Woods, MI**

**A.** There are several reasons why radical prostatectomy is probably not the most rational choice given the scenario described. First, high-grade tumors (Gleason score 7 or above) are more likely to have spread beyond the prostate at the time of diagnosis.

Second, older men with prostate cancer are more likely to have advanced disease than younger men—all other things being equal (Gleason score, PSA, stage). Third, the tumor has had four years to progress since diagnosis. Thus, surgery is unlikely to be curative. Lastly, surgery after radiation therapy is associated with a high risk of complications that could decrease quality of life without adding years to life.



## CONCLUSION

In this Special Report, we have covered in detail the current treatment options for recurrent prostate cancer. While it is true that there is currently no cure for recurrent cancer, new therapies and medications offer real hope for cancer remission, as do the results of some of the more promising clinical trials, without destroying the quality of life.

Men can live for many years with the disease, so depression and skeletal health issues are two other long-term aspects of recurrent cancer that need to be addressed sooner rather than later in the course of your prostate cancer treatment.

Each man faces prostate cancer in his own way, depending on age, overall health, initial treatment choice, and lifestyle considerations. We hope that the material presented here has given you a clear understanding of your range of options, so you can decide in conjunction with your doctors on the treatment regimen that is right for you.

As usual, my esteemed colleagues and I will continue to bring you the latest breaking news, findings, and recommendations concerning the diagnosis and treatment of prostate cancer in the quarterly *Johns Hopkins Prostate Bulletin*. Please feel free to contact us through Grand Rounds in the *Bulletin* with your questions and concerns.

We wish you the best of success in your personal fight against prostate cancer.

– Jacek L. Mostwin, M.D., D.PHIL. (OXON)



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# ADVANCED PROSTATE CANCER TREATMENTS

## HEALTH INFORMATION ORGANIZATIONS AND SUPPORT GROUPS

### American Cancer Society

1599 Clifton Rd. NE  
Atlanta, GA 30329  
☎ 800-ACS-2345

[www.cancer.org](http://www.cancer.org)

National, community-based organization that answers questions about cancer, provides information on specific cancer topics, and makes referrals to treatment centers or self-help organizations. Free publications on prostate cancer. Sponsors a support group called Man to Man.

### American Urological Association

1000 Corporate Blvd.  
Linthicum, MD 21090  
☎ 410-689-3700

[www.urologyhealth.org](http://www.urologyhealth.org)

Provides up-to-date doctor-reviewed information on adult and pediatric urological conditions.

### Cancer Care

275 7th Ave.  
New York, NY 10001  
☎ 800-813-HOPE/212-712-8400

[www.cancercare.org](http://www.cancercare.org)

Provides support for patients and families through financial assistance, educational materials, referrals to local community resources, and one-on-one counseling (at the 800 number).

### Cancer Information Service

National Cancer Institute  
6116 Executive Blvd., Room 3036A  
Bethesda, MD 20892-8322  
☎ 800-4CANCER

<http://cis.nci.nih.gov>

Nationwide network with 19 regional offices. Provides information about early detection, risk, and prevention of cancer; local services; and details of ongoing clinical trials. Publishes free literature.

### The National Kidney and Urologic Diseases Information Clearinghouse

3 Information Way  
Bethesda, MD 20892-3580  
☎ 800-891-5390

<http://kidney.niddk.nih.gov/>

National clearinghouse that provides access to a health information database. Also publishes a newsletter and provides educational material. Write, call, or visit the website for information.

### Prostate Cancer Education Council

5299 DTC Blvd., Ste. 345  
Greenwood Village, CO 80111  
☎ 866-477-6788/303-316-4685

[www.pcaaw.com](http://www.pcaaw.com)

The Council is a group of doctors and health professionals who produce educational materials on prostate cancer and are working on a long-term study on prostate screening.

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## LEADING HOSPITALS for Urology as Ranked by U.S. News & World Report

### 1. Johns Hopkins Hospital

Baltimore, MD  
☎ 410-502-4003/410-955-5464  
[www.hopkinsmedicine.org](http://www.hopkinsmedicine.org)

### 2. Cleveland Clinic

Cleveland, OH  
☎ 800-223-2273/216-444-2200  
[www.clevelandclinic.org](http://www.clevelandclinic.org)

### 3. Mayo Clinic

Rochester, MN  
☎ 507-284-2511  
[www.mayoclinic.org](http://www.mayoclinic.org)

### 4. University of California, Los Angeles, Medical Center

Los Angeles, CA  
☎ 800-825-2631/310-825-9111  
[www.healthcare.ucla.edu](http://www.healthcare.ucla.edu)

### 5. Memorial Sloan-Kettering Cancer Center

New York, NY  
☎ 800-525-2225/(212) 639-2000  
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## GLOSSARY

Here you will find dozens of prostate terms, organized and cross-referenced for your convenience. If a word used in a definition is in *italics*, that word has its own entry.

The terms are those most often used by urologists in describing prostate disorders.

### A

**Ablation:** Removal, elimination. For example, hormonal ablation means eliminating the androgens (male hormones) that nourish prostate cancer.

**Acid phosphatase:** An enzyme (such as *prostate-specific antigen*) that is secreted by the prostate gland. Elevated levels may indicate something is wrong with the prostate.

**Acute bacterial prostatitis:** A form of *prostatitis* associated with urinary tract infections. The ailment comes on quickly, accompanied by fever, pain in the perineum (area between the scrotum and rectum) and lower urinary tract symptoms that demand prompt medical attention.

**Adenocarcinoma:** A cancer originating in glandular tissue. Prostate cancer is classified as adenocarcinoma of the prostate.

**Adjuvant:** An additional treatment used to increase the effectiveness

of the primary therapy given concurrently or after the primary treatment. Hormonal therapy is often given concurrently with radiation therapy as an adjuvant therapy.

**Adrenal androgens:** Weak male hormones made by the adrenal glands. They include androstenedione, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEAS). Their overall effect on the prostate is controversial. Most (95 percent) of the testosterone in the blood comes from the testicles.

**Agonist:** A drug that triggers an action by a cell, another drug, or a hormone.

**Alpha blockers:** Medications, originally designed to treat hypertension, that act on the prostate by relaxing smooth muscle tissue within the prostate and at the bladder neck. Used to treat lower urinary tract symptoms in men with *BPH*.

**5-alpha reductase:** An enzyme in the prostate that converts testosterone to *DHT*.

**5-alpha reductase inhibitors:** Medications that block the formation of *DHT* by blocking the enzyme 5-alpha reductase, causing the prostate to shrink by about 20-30 percent. These drugs are used to treat lower urinary tract symptoms in men with *BPH*.

**Analgesic:** Painkiller.

**Analog:** A synthetic drug that can mimic one of the body's natural signaling molecules.

**Anal stricture:** Tight scar tissue that can interfere with a bowel movement.

**Androgen:** A substance with male hormone activity, such as *testosterone*.

**Androgen ablation therapy:** A treatment designed to inhibit the body's production of *androgens* (male hormones) or block the action of the androgen.

**Androgen-dependent, or -sensitive cells:** Prostate cancer cells that are dependent on male hormones for survival. These cells undergo *apoptosis* (cell death) when the hormones that nourish them are shut off.

**Androgen-independent, or -insensitive cells:** Prostate cancer cells that are *not* dependent on male hormones and therefore do not respond to hormone-blocking therapy by undergoing *apoptosis*.

**Angiogenesis:** The body's process of forming new blood vessels. Some anti-cancer drugs called angiogenesis inhibitors work by blocking angiogenesis, thus preventing blood from reaching and nourishing a tumor. Although the tumor may not die, its growth may be slowed or stopped.



**Antiandrogens:** Drugs such as bicalutamide and flutamide used in hormone therapy to treat prostate cancer. These drugs block or neutralize the effects of *testosterone* and *DHT* on prostate cancer cells by preventing testosterone and DHT from binding to the androgen receptor.

**Anticholinergic drugs:** A group of drugs that suppress bladder contractions. These medications may help some men with incontinence or overactive bladder.

**Anti-metastatic drugs:** Drugs that help prevent cancer from invading other cells or from developing new blood vessels (the process known as *angiogenesis*).

**Apoptosis:** Programmed cell death. The normal molecular mechanism that governs the life span of cells so that they die in a very organized fashion.

**Artificial sphincter:** A surgically-implanted device used to treat severe incontinence that has persisted for a year or longer and shows no signs of improving.

**Asymptomatic:** Experiencing no symptoms.

**Atypical:** A finding on a prostate biopsy meaning the cells do not look normal but are not necessarily cancerous.

## B

**Benign:** Harmless; not cancerous.

**Benign prostatic hyperplasia:** See *BPH*.

**Biochemical failure:** Residual prostate cancer detected by a rising *PSA* after treatment.

**Biopsy of the prostate:** The removal of tissue from the prostate so it can be examined for the presence of cancer. This is performed using *transrectal ultrasound (TRUS)* guidance.

**Bladder:** The hollow, muscular reservoir that functions as a holding tank for urine.

**Bladder neck:** The junction between the bladder and the prostate.

**Bladder neck contracture:** Constriction of the *bladder neck*, generally by scar tissue. This can block urine flow.

**Bladder stones:** These may occur when urine in the bladder is concentrated and compounds (such as calcium and uric acid) crystallize.

**Bone scan:** Diagnostic image of the skeleton, used for detecting the spread of cancer to the bone through the use of radioactive tracers injected into the bloodstream. Also called radionuclide scintigraphy.

**“Bound” PSA:** *PSA* molecules in the bloodstream that are chemically tied to proteins. Other *PSA* molecules without chemical ties are called “free.” If a man has a *PSA* test and most of the *PSA* is bound,

the *PSA* elevation is more likely linked to cancer.

**BPH:** Benign prostatic hyperplasia, a non-cancerous condition of the prostate that is more common in older men. It results in a growth of prostate tissue around the urethra and an increase in the size of the prostate gland.

**Brachytherapy:** A form of radiation therapy in which radioactive pellets (“seeds”) are implanted into the prostate to deliver radiation directly to the tumor sites. Also called interstitial brachytherapy.

## C

**Capsule of the prostate:** The outer wall of the gland.

**Carcinoma:** A malignant tumor made up chiefly of epithelial cells. See **adenocarcinoma**.

**Castrate range:** The level to which the body’s testosterone drops after orchiectomy. This is an important factor in monitoring hormone therapy, as certain drugs are judged by their ability to reduce testosterone to this range.

**Castration:** See *orchiectomy*.

**Catheter:** A tube used for drainage or irrigation, most commonly to drain urine out of the bladder.

**CAT (CT) scan:** See *computed tomography*.



**CGy:** Abbreviation for centigray; a unit of radiation equivalent to the older unit called a “rad.”

**Chemical castration:** The use of drugs to lower testosterone to the *castrate range*.

**Chemotherapy:** The treatment of cancer using chemicals to deter or stop the growth of cancer cells.

**Chronic bacterial prostatitis:** A form of *prostatitis* associated with urinary tract infections. Diagnosis is based on positive cultures that identify bacteria in the prostate, and an abundance of white blood cells in prostatic secretions. This illness may recur periodically after an initial acute episode.

**Chronic prostatitis/chronic pelvic pain syndrome:** The most mysterious category of *prostatitis*. The causes of symptoms are not known. In some men, the prostate may not even be the problem with pain coming from the lower back, pelvis, or rectum. This category has two subgroups—inflammatory and noninflammatory, based on whether any white blood cells can be found in the prostatic fluid.

**Clinical trial:** A type of research study designed to test a new approach (prevention or treatment) to a disease in people. The study is overseen by the Institutional Review Board of the institution where the study is being carried out, or the Food and Drug Administration. There are typically three phases in the clinical trial that must be passed

before a new drug or device is approved.

**Combination therapy:** A form of *hormonal therapy* that surgically or chemically blocks the production of *testosterone* by the testes, and involves the additional use of an *anti-androgen* to block the receptor sites from utilizing *adrenal androgens*.

**“Complexed” PSA (cPSA):** The same as *bound PSA*.

**Computed tomography:** The use of special x-ray equipment to obtain image data from different angles around the body together with computer processing of the information to render a cross-section of body tissues and organs. Also referred to as cross sectional imaging or CT or CAT scan.

**Conformal radiation therapy:** A technique for delivering *external-beam radiation* precisely to a target (e.g., the prostate), while minimizing damage to nearby healthy tissue.

**Corpora cavernosa:** Spongy chambers in the penis that become engorged with blood during an erection.

**Creatinine test:** A blood test that helps check kidney function.

**Cryotherapy:** The use of liquid nitrogen probes to freeze tissues or organs (e.g., the prostate), causing cancer cells within the gland to rupture and die as they begin to thaw.

**CT scan:** See *computed tomography*.

**Cystometry:** A urological test that measures bladder pressure and function using a pressure sensing catheter that is passed through the urethra into the bladder.

**Cystoscope:** An optical instrument consisting of a tiny lighted tube that is usually passed through the *urethra* into the *bladder*, allowing for inspection of the bladder, prostate, and urethra for abnormalities.

**Cytokine:** A chemical messenger protein released by white blood cells. Cytokines facilitate communication among immune system cells and between immune system cells and the rest of the body.

## D

**DES (diethylstilbestrol):** A synthetic female hormone used until 1971 to prevent miscarriages, but taken off the market when it was found to cause birth defects. Now used in lower doses as a form of hormone therapy for men with advanced prostate cancer.

**DHT (dihydrotestosterone):** The most potent form of androgen in the prostate derived from conversion of *testosterone* by an enzyme known as *5-alpha reductase*.

**Digital rectal examination (DRE):** An uncomfortable but not painful screening procedure in the urological examination during which the physician inserts a gloved, lubricated finger into the rectum to examine the prostate gland for enlargement, lumps, or hard areas.



**Diuretics:** Medications that alter water absorption by the kidney. These drugs cause the kidneys to absorb less water, so more of it leaves the body in the form of urine.

**“Dry” orgasm:** An orgasm that occurs without the expulsion of seminal fluid (ejaculation) either because seminal fluid is no longer produced (e.g., after surgical removal of the prostate and seminal vesicles for prostate cancer), or because the fluid travels backwards into the bladder (retrograde ejaculation) due to an abnormality or absence of the bladder neck. Surgery (e.g., TURP) and drugs can result in retrograde ejaculation.

## E

**Ejaculate:** Seminal fluid produced by the prostate and seminal vesicles that transports sperm at the time of orgasm.

**Endothelin:** A family of proteins considered the most potent stimulants of blood vessel constriction. These proteins are thought to play an important role in the bone pain that results from metastatic prostate cancer.

**Epithelial cells:** Cells that line the lumen (inside) of glandular tissue like the prostate and are responsible for production of the secretory fluid produced by the gland (e.g., seminal fluid).

**Erectile dysfunction (ED):** An inability to obtain or maintain an erection suitable for penetration.

**Estrogens:** Female hormones. Estrogens can block the release of luteinizing hormone (*LH*)—the protein produced in the pituitary that signals the testicles to produce testosterone—and can lower testosterone to the castrate range. The main oral estrogen is *DES* (diethylstilbestrol).

**Expectant management:** A management option for prostate cancer in which patients (usually older age) are monitored for the progression of cancer without undergoing active treatment (surgery, radiation, or hormonal therapy). Formerly called “watchful waiting.”

**External-beam radiation therapy:** Treatment to kill cancerous tissue from outside the body by focusing a high-powered X-ray beam on the affected area a few minutes at a time, usually over the course of weeks.

## F

**Flomax (tamsulosin):** A popular *alpha-blocker* drug used to treat lower urinary tract symptoms in men with *BPH* by relaxing prostate and bladder neck smooth muscle.

**Flutamide:** The generic name of Eulexin. An *anti-androgen* used to treat advanced prostate cancer.

**Foley catheter:** A catheter inserted through the urethra into the bladder where it is held in place with a tiny, inflated balloon. It drains urine from the bladder and can be used to irrigate the bladder free of blood clots.

**Fosamax (alendronate sodium):** A drug used to treat osteoporosis.

**Free prostate-specific antigen (PSA) test:** A blood test that measures how much *PSA* is not bound to blood proteins (free). The lower the percentage of free *PSA* the higher the chance that prostate cancer is present.

**Frozen sections:** A technique in which removed tissue from the body is frozen, cut into very thin slices, and stained for microscopic examination by a pathologist. Physicians sometimes use frozen sections to analyze tissues while surgery is taking place. Frozen sections are rarely used during prostate surgery today.

**FSH:** Follicle-stimulating hormone, made along with *LH* by the pituitary gland. *FSH* has its major effect on the testicular cells that make sperm; whereas *LH* acts on the cells that produce testosterone.

## G

**Gene therapy:** A technique for correcting defective genes responsible for disease development by inserting normal or genetically-altered genes into cells.

**Gleason score:** A method for grading the cellular differentiation of prostate cancer based on how it looks under the microscope. In general, well-differentiated cancers are less aggressive than poorly differentiated cancers. Prostate cancers are usually composed of cells with multiple grades from 1 to 5 with higher grades representing



more poorly differentiated cells. A Gleason score is derived from combining the two most prevalent grades (1 to 5) within the tumor resulting in a score of 2 to 10 (e.g., 3 + 4 if the most prevalent grade was 3 and the second most prevalent grade was 4). Cells that are well-differentiated are given a low grade, ranging from 2 to 4. Moderately well-differentiated cells fall in the middle, with grades of 5 to 6. Poorly differentiated cells have high grades of 7 to 10.

**Gynecomastia:** Tenderness, pain, or swelling of the breasts in men. This is a treatable side effect of some forms of hormone therapy.

## H

**Hematuria:** Blood in the urine.

**Hereditary prostate cancer (HPC):** A term used to describe a family that is thought to have a heritable form of prostate cancer transmitted from generation to generation. A definition of HPC that is commonly used is the family in which prostate cancer is present in three first-degree relatives (a father or brothers)—or two first-degree relatives, if both developed it before age 55—or, if prostate cancer has occurred in three generations in the family (grandfather, father, son). The cancer can be inherited from either side of the family.

**Hormone-refractory prostate cancer:** *Metastatic* prostate cancer that is no longer responsive to hormonal therapy usually manifested by a rising PSA.

**Hormonal therapy:** A treatment that uses drugs to deprive the prostate of androgens. Some cancerous prostate cells are responsive to the therapy, others are not.

**Hot flash:** A side effect of some forms of hormonal therapy for prostate cancer that results in a sudden rush of warmth to the face, neck, and upper body, lasting anywhere from minutes to hours.

**Hyperplasia:** An increase in the number of cells in the prostate.

## I

**Immunotherapy:** Treatments designed to maximize the ability of the immune system to fight cancer.

**Incontinence:** The involuntary loss of urinary control. Also called urinary incontinence.

**Insulin-like growth factors:** A class of proteins that promote cell proliferation and may influence the development of prostate cancer.

**Intensity modulated radiation therapy (IMRT):** The newest form of delivering *external beam radiation* that allows for more precise delivery of calculated radiation dosage to the selected target.

**Intermittent hormonal therapy:** An approach to hormonal therapy whereby PSA levels are used as a trigger to stop and start *androgen ablation*. When PSA levels begin to drop therapy is discontinued and initiated again when PSA levels begin to rise.

**Irritative lower urinary tract symptoms:** Bothersome symptoms including some or all of the following: Frequent urination that can occur both day and night (*nocturia*); a strong sense of urgency to urinate; inability to postpone urination; pain with urination.

**Isoflavones:** Natural compounds found in soy products that have been promoted as anticancer agents.

## K

**Kegel exercises:** Special exercises to strengthen the pelvic floor muscles that help control urination.

**Kidneys:** The paired organs primarily responsible for making urine that helps the body dispose of the by-products of metabolism, the body's mechanism for maintaining function of tissues.

## L

**Laparoscopy:** A technique in which a tiny instrument containing a light and camera at one end is inserted into the body through a small incision. Used for a variety of surgical and diagnostic procedures, including *radical prostatectomy*.

**Latent:** Dormant.

**LH (luteinizing hormone):** A chemical substance transmitted by the pituitary gland that causes the testes to make testosterone.

**LHRH (luteinizing hormone-releasing hormone):** A chemical signal (protein) originating in the



hypothalamus portion of the brain that causes the pituitary gland to make *LH* and *FSH*.

**LHRH agonists:** Synthetic versions of the body's *LHRH* that can block pituitary production of *LH* and therefore, testosterone production.

**Libido:** Sex drive.

**Localized prostate cancer:** Cancer that is thought to be confined to the prostate gland, and therefore considered curable.

**Lupron (leuprolide acetate):** The brand name of an *LHRH* agonist used in hormone therapy.

**Lymph node:** A bean-shaped tissue found throughout the body that is part of the immune system. The lymph nodes trap foreign substances (e.g., bacteria) keeping them from spreading to other areas of the body.

## M

**Magnetic Resonance Imaging (MRI):** A painless, non-invasive technique using equipment that produces strong magnetic fields to yield detailed three-dimensional images of internal body structures.

**Malignant:** Abnormal growth associated with the ability of cells within the tissue to spread beyond the organ of origin (become *metastatic*).

**Medical castration:** The use of medication to interfere with the manufacture or actions of *testosterone*.

**Metastasis, metastases, metastatic:** Cancer that has spread from the original tumor site and established itself elsewhere. *Metastases* is plural, and *metastatic* is the adjective form.

**Middle lobe enlargement:** Growth of prostate tissue that extends inside the bladder. When it enlarges, it can block the opening of the bladder like the cork in a bottle.

**Morbidity:** The rate at which disease occurs.

**MRI:** See *Magnetic Resonance Imaging*.

## N

**Nadir:** The lowest point. When **PSA** is recorded over a period of time, the lowest number would be the nadir.

**“Nerve-sparing” radical prostatectomy:** The anatomical approach to *radical retropubic prostatectomy*, which includes important modifications to reduce blood loss, preserve urinary control, and preserve delicate nerves essential for erections.

**Neurovascular bundles:** Cordlike conduits located on the rectum beside the prostate that contain blood vessels and the microscopic nerves essential for erections.

**Nitric oxide:** A signaling molecule released by nerve endings during erection that allow the smooth muscle tissue in the penis to relax.

**Nocturia:** Frequent urination during the night.

## O

**Obstructive lower urinary tract symptoms:** Includes weak urine flow; hesitancy in beginning urination; pushing or straining to start urine flow; intermittent urine stream; a sense of not being able to completely empty the bladder.

**Oncology:** The study and treatment of benign (non-cancerous) and malignant (cancerous) growths. An oncologist (surgical, radiation, or medical) is a specialist in the study of and treatment of cancerous tumors.

**Orchiectomy:** Surgical castration. A form of hormone therapy involving removal of all or part of the testicles. This causes testosterone to fall to the *castrate range*.

## P

**Palliative:** Treatment that makes symptoms better but not designed to treat the underlying cause of these symptoms.

**Pathologist:** A doctor who examines tissues removed from the body to help determine a diagnosis, stage, and prognosis of a disease process like cancer.

**Penile implant:** Mechanical prosthesis that enables a man with *erectile dysfunction* to have erections.

**Perineum:** The area between the rectum and the scrotum.



**Perineural invasion:** Prostate cancer in the spaces around the nerves within the prostate, not nerves outside the prostate (e.g., neurovascular bundles).

**Peripheral zone:** The area of the prostate contiguous with the rectum and where most prostate cancers arise.

**Peyronie's disease:** An abnormal curvature of the penis due to an abnormal deposition of fibrous tissue in the elastic covering (tunica albuginea) surrounding the corporal penile bodies (cavernosa). The cause is unknown.

**Phosphodiesterase inhibitors:** Vasoactive drugs such as Viagra, Levitra, and Cialis that can enhance the penile erectile response to stimulation.

**Phytotherapy:** The use of plant-derived substances to treat medical conditions such as *benign prostatic hyperplasia (BPH)*.

**PIN (prostatic intraepithelial neoplasia):** Abnormal prostate epithelial cells found on biopsy that are believed to be precancerous.

**Placebo:** A non-active "pill or capsule" often given to subjects in a medical study that comprise the control group against which those taking the study drug are compared.

**Prostate membrane specific antigen (PMSA):** A protein that is made by prostate cancer cells and expressed on the surface of the cells.

**Pressure-flow studies:** A test to monitor bladder pressure changes as a man urinates. See *cystometry*.

**Proctitis:** Inflammation of the lining of the rectum.

**ProstaScint:** A test for detecting prostate cancer that has spread to other parts of the body (except the bones).

**Prostate:** A walnut-shaped gland about an inch and a half long that sits directly under the bladder. Its main function is to make part of the seminal fluid for sperm transport.

**Prostate capsule:** The outer covering of the prostate gland.

**Prostate Specific Antigen (PSA):** A protein made by both benign and cancerous prostate epithelial cells. The PSA test is a blood test that measures levels of PSA in the blood. An elevated reading indicates an abnormal condition of the prostate gland, either benign or malignant. The PSA test is the best tumor marker for the identification and monitoring of prostate cancer.

**Prostatectomy:** Surgical removal of all or part of the prostate gland. A simple prostatectomy removes the inner portion of the prostate to relieve obstruction from *BPH*; whereas a *radical prostatectomy* removes the entire prostate and *seminal vesicles* to treat prostate cancer.

**Prostatic calculi:** Tiny, generally

harmless stones found in the prostate. When they become infected, as they often do in men with chronic bacterial prostatitis, they can cause a lingering infection.

**Prostatitis:** Inflammation of the prostate.

**Proton-beam radiation:** A form of external-beam radiation therapy that uses charged particles instead of electromagnetic waves to deliver ionizing radiation.

**PSA:** See *prostate specific antigen*.

**PSA density:** The PSA level divided by the volume of the prostate, as determined by *transrectal ultrasound*.

**PSA velocity:** The change in PSA between measurements divided by the elapsed time between the measurements.

## R

**Radiation therapy:** Use of ionizing radiation to destroy cancer cells by damaging DNA within the cells. See *external-beam radiation* and *interstitial brachytherapy*.

**Radical prostatectomy:** A surgical procedure to remove the entire prostate gland and *seminal vesicles* to treat prostate cancer.

**Recurrence:** Evidence for residual prostate cancer following treatment usually manifested today as a rising *PSA*. Local recurrence indicates a return of the cancer in the



pelvis either in the prostate or in the area of the prostate; whereas distant recurrence indicates the presence of disease beyond the pelvis in lymphatic tissues or bone.

**Refractory:** No longer responsive to therapy.

**Resection:** The surgical removal of tissue.

**Retrograde ejaculation:** See *dry orgasm*.

**Retropubic prostatectomy:** Surgical removal of all or part of the prostate gland through an incision in the lower abdomen above the pubic bone. Radical retropubic prostatectomy is removal of the prostate and seminal vesicles to treat cancer; and simple retropubic prostatectomy is removal of the inner portion of the prostate to treat enlargement causing urinary obstruction.

## S

**“Salvage” therapy:** Secondary treatment for recurrence of cancer.

**Saw palmetto:** An extract from the berries of the sabal palm growing in southeastern U.S. that can reduce lower urinary tract symptoms in some men.

**Selenium:** An essential mineral in the body that is part of antioxidant enzymes and necessary for normal function of the immune system. It is primarily found in plant foods and may play a role in prostate cancer prevention.

**Semen:** The fluid that transports sperm.

**Seminal vesicles:** Glands that, like the prostate, support male reproduction by producing seminal fluid for transport and maintenance of sperm.

**Sextant biopsy:** A procedure in which six samples of cells are taken from the prostate, one each from the top, middle, and bottom of the gland, on the right and left sides. Sextant biopsies are now thought to be inadequate for diagnosing prostate cancer.

**Spinal cord compression:** The collapse of bone surrounding the spinal cord (vertebrae) due to destruction by *metastatic cancer* that can result in nerve damage and loss of motor and sensory body functions.

**Sphincter:** A circular muscle that contracts to close an orifice. The urethral sphincter closes the bladder outlet and contributes to urinary control.

**Spot radiation:** Localized external-beam radiation treatment designed to target one or several painful bone metastases. While it can relieve pain in treated sites, it cannot prevent new metastases from appearing in bone.

**Stage of prostate cancer:** The extent of the disease determined by physical examination, scans, and/or direct assessment of removed lymph nodes and prostate tissue that helps a physi-

cian determine the prognosis and appropriate treatment.

**Stress incontinence:** The involuntary leakage of urine during activities that increase pressure inside the abdomen (e.g., bending, laughing, exercising).

**Stricture:** Narrowing caused by scar tissue that can lead to blockage.

**Surgical castration:** Surgical removal of either the *testicles* (bilateral *orchiectomy*) or the contents of the testicles (subcapsular orchiectomy).

**Surgical margins:** The borders established when pathologists look at the edges of tissue that has been removed during surgery. If no cancer appears on these edges and the margins are “clear,” or “negative,” then there is a higher likelihood that all cancerous tissue was removed. However, if the margin is “positive,” there is a lower likelihood that all cancer was removed.

## T

**Testicles:** Paired male organs lying within the scrotum responsible for production of sperm and the male hormone testosterone. Hormones produced in the brain modulate testicular function.

**Testosterone:** The male hormone, or **androgen**, that is responsible for many male traits including libido (sexual drive), and the maintenance of prostate function. Lowering testosterone results in regression of prostate tissues



including prostate cancer cells and is a major goal of hormone therapy used to treat prostate cancer.

**Thermal therapy (thermotherapy):**

Using heat to destroy tissue. Transurethral Microwave Thermotherapy (TUMT) and Transurethral Needle Ablation (TUNA) are methods for transmitting heat to the prostate for the treatment of lower urinary tract symptoms due to *benign prostatic hyperplasia (BPH)*.

**Three-dimensional conformal radiation:**

An approach to external-beam radiation therapy in which many X-ray beams, shaped to fit the target area, are focused on the prostate to deliver a high dose of radiation, with minimal damage to nearby healthy tissue.

**TNM system:** A system for describing the clinical stage of a cancerous tumor using T numbers (T1 to T4) to indicate whether the tumor can be felt or not and if it can be felt, the extent of the tumor. In addition, an N+ is used to indicate cancer that has spread to the lymph nodes and an M+ for cancer that has spread to other parts of the body.

**Total androgen blockade:** An approach to the treatment of advanced prostate cancer that includes shutting off the production of testosterone by the testicles (either surgically or medically), and blocking the action of other androgens (from the adrenal glands) using drugs that bind to androgen receptors.

**Transition zone:** The interior portion of prostate tissue surrounding the urethra that grows and enlarges in men with *benign prostatic hyperplasia (BPH)*.

**Transrectal ultrasound (TRUS):**

An examination of the prostate with a small probe placed in the rectum. The probe emits high-frequency sound waves aimed at the prostate that are used to construct images of the prostate gland and surrounding structures. TRUS is used by urologists and radiologists to determine the size of the prostate and direct the needle used in prostate biopsies.

**Transurethral incision of the prostate (TUIP):**

A *benign prostatic hyperplasia (BPH)* treatment in which one or two small incisions are made in the prostate with an electrical knife or laser. Decreasing the pressure the prostate exerts on the urethra alleviates symptoms of BPH.

**Transurethral microwave therapy (TUMT):**

A *benign prostatic hyperplasia (BPH)* treatment that uses microwave energy to heat and destroy prostate tissue. The microwave energy is emitted from a catheter inserted in the urethra.

**Transurethral needle ablation (TUNA):**

A *benign prostatic hyperplasia (BPH)* treatment in which prostate tissue is destroyed with heat delivered by low-energy radio waves through tiny needles at the tip of a catheter inserted into the prostate through the urethra.

**Transurethral resection of the prostate (TURP):**

A procedure used to treat lower urinary tract symptoms due to benign prostatic hyperplasia (BPH) in which prostate tissue is removed (resected) with an instrument that is passed through the urethra.

**Tumor:**

An excessive accumulation of cells within an organ that occurs when the normal mechanisms controlling cell replacement are lost. Tumors that are benign do not have the ability to produce cells that spread beyond the organ of origin (become metastatic or metastasize); whereas malignant tumors possess the ability to metastasize.

## U

**Ureters:** The conduits for transport of urine from the *kidneys* downward to the bladder.

**Urethra:** The tubular structure from the bladder that traverses the penis and carries urine from the bladder, and seminal fluid from the prostate and seminal vesicles out of the body.

**Urethral sphincter:** The muscular structure responsible for preventing urinary leakage.

**Urethral stricture:** Scar tissue that can block the urethra and prevent the normal passage of urine.

**Urge incontinence:** A sudden need to urinate accompanied by a bladder contraction, resulting in an involuntary loss of urine.



**Urinalysis:** Microscopic examination of urine.

**Urinary catheter:** A thin, flexible tube that can be passed into the bladder through the urethra to allow the urinary tract to heal around it after surgery, or to monitor the output of urine.

**Urinary retention:** Inability to urinate either due to a blockage in the urinary tract, or inadequate contraction of the bladder or relaxation of the urinary sphincter.

**Urodynamic studies:** Tests that evaluate the pressures generated by the bladder to expel urine and

the flow of urine in order to determine the cause of lower urinary tract dysfunction.

**Urologist:** A surgeon that specializes in the diagnosis and treatment of male and female urinary tract disease, and male reproductive disease.

**UTI: Urinary tract infection.** The presence of bacteria in the urinary tract that cause inflammation. The inflammation of the urinary tract can cause fever, pain, and lower urinary tract symptoms, such as frequency and urgency.

## V

**Vacuum erection device:** A tubular device placed over the penis that creates a vacuum, drawing and trapping blood within the penis to produce an erection.

**Vasodilator:** A drug that allows the penis to become engorged with blood by widening the blood vessels. Used as a treatment for erectile dysfunction (ED). (tension, or hormonal therapy).



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