



Report to the Nation on **Prostate Cancer**

A Guide for Men and Their Families

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Prostate Cancer Foundation

The Prostate Cancer Foundation (PCF) is the world's largest philanthropic source of support for prostate cancer research. Founded in 1993, the PCF has raised more than \$230 million and provided funding for prostate cancer research to more than 1200 researchers at 100 institutions worldwide.

The PCF has a simple yet urgent goal: to find better treatments and a cure for recurrent prostate cancer. The PCF pursues its mission by reaching out to individuals, corporations, and others to marshal support for prostate cancer research. The PCF then provides funding for cutting-edge prostate cancer research and works with research scientists, physicians, government officials, biopharmaceutical industry executives, and others to remove barriers that impede progress toward a cure. The PCF also advocates for greater awareness of prostate cancer and more governmental resources for fighting the disease. For more information, visit <http://www.prostatecancerfoundation.org>.

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Foreword

Receiving a diagnosis of prostate cancer typically raises numerous concerns and questions about how to best treat the disease and how it will impact the future. Can I be cured? What is my prognosis? How will the treatment that I choose affect my lifestyle? What questions should I be sure to ask my doctors? How do I make treatment choices for a disease I know little about? Every day, hundreds of men are diagnosed with prostate cancer, and they and their families start looking for answers to complex questions such as these.

Report to the Nation on Prostate Cancer: A Guide for Men and Their Families is designed to help you and your fellow prostate cancer survivors through this process, by teaching you what you need to know about the disease and the different treatments. The four authors of this guide — one urologist, one medical oncologist, one radiation oncologist, and one oncology nurse — highlight what to consider at each step of the way based on their decades of collective experience treating and educating men with prostate cancer. But perhaps most importantly, they will show you how to work together with all of the members of your health care team to find the treatment path that's right for you.

The Prostate Cancer Foundation has spent the past 12 years raising money and funding the work of the best and the brightest researchers in prostate cancer today. We are proud to have played a role in identifying new therapeutic strategies and approaches for men with prostate cancer, and are proud to play a role in helping you to understand what to expect throughout the course of your disease and how to optimize the outcomes of your treatment.

On behalf of the esteemed authors, the men and women who have who have dedicated their lives to prostate cancer research, and the many donors and supporters who have given of their resources to make this program possible, we extend our best wishes for your health. It is our hope that this *Guide* will help you work with your doctors to navigate your way toward a better and longer life, spending less time focusing on prostate cancer and spending more time enjoying life with your family and friends.



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Introduction

In preparing this *Report to the Nation on Prostate Cancer: A Guide for Men and Their Families*, we had one goal: to arm you with as much as information as possible about prostate cancer and its treatments so you can work with your doctors to choose the path that's right for you.

But achieving this goal was not easy. We knew that if we had offered a complete and comprehensive look at every treatment option, few would be interested in reading it. On the other hand, offering a brief review that did not explore the often nuanced differences between treatment options would not be helpful either.

We therefore did our best to highlight the key issues that you'll face over the years, to focus on how the results of lab tests or scans might affect the way your cancer is managed, and to emphasize the importance of working together with all members of your health care team at every step of the way.

Fortunately, there are a variety of treatment options at every stage of prostate cancer, but new decisions about each option will be required at every step along the way. Because different therapies are offered by different specialists, we encourage you to assemble a team of specialists, including a urologist, a radiation oncologist, and a medical oncologist with whom you can discuss the different treatment options and find the path that's right for you.

We have divided this guide into three sections, each representing a different stage of disease progression, and have included a set of tear-out sheets and wallet-sized cards for each stage that you can carry with you, summarizing key points to consider and questions to ask your doctors. The final section gives you an opportunity to look ahead to the future, to see what the new research is focusing on, and to learn about whether enrolling in clinical trials and joining in the fight against prostate cancer might be right for you.

It is our hope that this *Guide* will enable you to hold meaningful, regular dialogues with the doctors, nurses, and pharmacists who have dedicated themselves to ensuring that you and your fellow prostate cancer survivors will live longer and better lives.

The first section of the *Guide* focuses on what you need to know when you've been diagnosed with early-stage prostate cancer. In Chapter 1, we review the ways in which doctors can use the tumor samples that they've taken in the biopsy, your PSA, and a number of other factors to determine how your cancer is likely to act over the coming years. In Chapters 2 and 3, we go over the ins and outs of each of the different treatment options for localized prostate cancer — active surveillance, surgery, and radiation therapy, reviewing the procedures themselves and the most common side effects. In Chapter 4, we remind you of the small but significant changes that you can make in your diet and lifestyle to keep you strong and healthy during the course of your disease.

The second section of the *Guide* focuses on what you need to know if your PSA starts to rise after initial therapy. In Chapter 5, we review what a PSA rise means at this stage of the disease, and describe the possible use of a second local therapy to destroy or remove the cancer that might be growing. In Chapter 6 we talk about hormone therapy — we describe the different types of drugs and how they work, and look at how doctors and researchers are working hard at trying to minimize the effects that the drugs will have on your quality of life.

The third section of the *Guide* focuses on what you need to know if your PSA starts to rise while you're on hormone therapy. In Chapter 7, we explain why and how the different chemotherapy drugs are used, and review the principles of dealing with side effects from the different drugs. Finally, in Chapter 8, we discuss the challenges that men with prostate cancer bone metastases face in their every day lives, review some of the available treatment approaches, and offer some insight into how effective pain management strategies can help them stay strong to fight their disease.

As we noted above, in the fourth and final section we look ahead to the future of prostate cancer research. Chapter 9 reviews some of the new and upcoming therapeutic approaches and treatment strategies for men with prostate cancer, and Chapter 10 describes the process by which these new treatments move from the lab to the clinic. None of these new therapies can be proven safe and effective for men with prostate cancer without the help of the thousands of

men each year who enroll in clinical trials and join the fight against the disease. At each step of the way, discuss with your doctors whether enrolling in a clinical trial is right for you. Your participation can help us find better treatments and, ultimately, a cure for prostate cancer.

We hope that the knowledge you gain from the information in this *Guide* will enable you to be an active participant in your prostate cancer treatment planning. Remember that there is no one-size-fits-all solution or approach to treating prostate cancer at any stage of the disease. The key is to stay focused on your unique circumstances and to work with members of your healthcare team to find the treatment path that's right for you.



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CHAPTER 1

What Does a Diagnosis of Prostate Cancer Mean?

Being diagnosed with cancer is a life-changing experience. It requires you to start making some hard decisions that can affect your daily life in significant ways for many years to come.

If you or someone you love has been diagnosed with prostate cancer, you'll be faced with a number of different therapy options, all of which might be equally effective, but each of which also has its upsides and downsides. More than 200,000 men in the United States will be diagnosed with prostate cancer this year, and each and every one of them will need to make very personal and individualized decisions about which treatment might be right for him. Do I undergo treatment? If yes, which treatment? Surgery? External radiation? Radiation seed implantation? Hormones? Chemotherapy? Or is active surveillance the right choice?

In this Chapter, we'll review the basic background material you need to know about a diagnosis of prostate cancer. We'll talk about PSA (prostate specific antigen) and Gleason score, which factors might be important in determining outcomes and prognosis, and, most importantly, we'll talk about why you need to surround yourself with a team of prostate cancer experts, comprising a wide variety of practice specialties, to help you find the path that's right for you.

Making Sense of the Diagnosis

If you're like many other men who are diagnosed with prostate cancer, you went to your doctor for a routine check-up and had a PSA and DRE (digital rectal exam) to screen for prostate cancer. Something irregular showed up, and your doctor sent you for a biopsy. Then, a few days after the biopsy, you were told that prostate cancer was found. Or, you might have noticed changes in your urinary or sexual function and asked your doctor about it. Then, after a full work-up, including a biopsy, the diagnosis of prostate cancer was made.



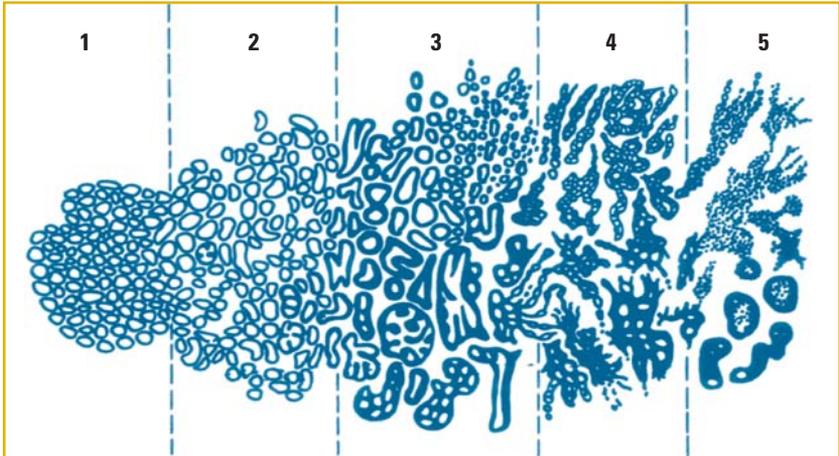
But what exactly did the doctor looking at your biopsy see? Why is it important for you to know what your tumor cells look like? After all, cancer is cancer, right?

In fact, the way your cells look under the microscope can tell a lot about your disease, and will often drive some very important decisions about treatment options.

Under normal conditions, your prostate cells, just like all other cells in your body, are constantly reproducing and dying. And each new prostate cell that grows has the same shape and appearance as all of the other prostate cells. But cancer cells look different, and the degree to which they look different from normal cells is what determines the cancer *grade*. Low-grade tumor cells tend to look very similar to normal cells, whereas high-grade tumor cells have mutated so much that they often barely resemble the normal cells.

The *Gleason grading system* accounts for the five distinct patterns that prostate tumor cells tend to go through as they change from normal cells. The scale runs from 1 to 5, where 1 represents cells that are very nearly normal, and 5 represents cells that don't look much like prostate cells at all.

Gleason grading describes how closely prostate cancer cells resemble normal prostate cells



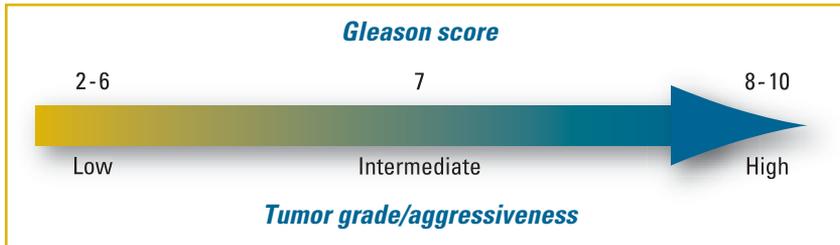
Source: Gleason DF. Histologic grading and clinical staging of prostatic carcinoma. In: Tannenbaum M, ed. *Urologic Pathology: The Prostate*. Philadelphia: Lea & Febiger, 1977;171.

After examining the cells under a microscope, the pathologist looking at your biopsy sample assigns one Gleason grade to the

most common pattern, and a second Gleason grade to the next most common pattern. The two grades are added, and your Gleason score, or sum, is determined.

Generally speaking, the Gleason score tends to predict the aggressiveness of the disease and how it will behave in your body. The higher the Gleason score, the less the cells behave like normal cells, and the more aggressive the tumor tends to be.

Gleason scores indicate the aggressiveness of the tumor



Remember, the Gleason score is not just a single number. It's composed of the two most common Gleason patterns recognized, and the first number, representing the most common pattern, is often more important. So although two *scores* might be the same, the underlying *grades* might be different, and, therefore, the tumor characteristics might be different. For example, a Gleason 7 (3+4) cancer would likely prove to be less aggressive than a Gleason 7 (4+3) cancer, even though, technically speaking, both have the same Gleason score.

In some cases, the pathologist might identify a third pattern, which is less common but that has a higher grade than either of the first two patterns that comprised the Gleason score. The presence of this third pattern might indicate that the tumor is more aggressive than the Gleason score would otherwise imply. For example, if a Gleason 4+3 tumor also has some grade 5 cells, the cancer would be considered as being of higher grade disease overall.

Where Does PSA Fit In?

PSA, or prostate specific antigen, is a protein produced by the prostate and released in very small amounts into the bloodstream. When there's a problem with the prostate, such as when prostate

cancer develops and grows, more and more PSA is released, until it reaches a level where it can be easily detected in the blood. PSA plays two different roles in prostate cancer — first as a screening tool before the disease is diagnosed, and then as a way to monitor progression of the disease once it's been established.

PSA is used as both a screening tool before the disease is diagnosed and as a way to monitor disease progression once it's been established.

In this *Guide*, we'll be focusing on the role of PSA as a marker for disease progression and as a way of determining whether a treatment is effectively doing its job. You might have been following the debates concerning the value of PSA in

screening for prostate cancer. For you, this is no longer an issue. Now that you've been diagnosed with prostate cancer, you need to shift gears and focus on how to best treat your disease.

So how does your PSA fit in with your Gleason score?

The PSA level that you had before you were diagnosed with prostate cancer, known as your prediagnostic PSA, is often used as an indicator of how advanced your cancer was before it was detected. Usually, the higher the prediagnostic PSA, the more aggressive the disease, the same as with the Gleason grade.

Therefore, this PSA level, combined with your Gleason score, is typically used when trying to predict how your tumor will respond to different types of treatment, and how well you're likely to fare following initial therapy. And, as we'll see, having a general sense of what to expect can help you and your doctors figure out which treatment path is right for you.

Predicting Prognosis

Despite the best efforts of hundreds of prostate cancer researchers, there's no way to know for certain exactly how your tumor will act and exactly how you will respond to any particular treatment or intervention. Our understanding of the way the disease behaves is getting better all the time. But, for now, we need to be able to predict, as best we can, what to expect so that we can determine the treatment that's right for you.

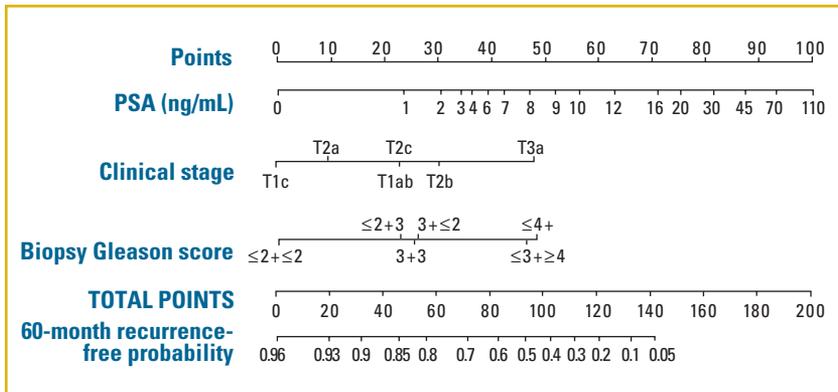
Suppose you wanted to estimate how likely it is that a particular treatment will get rid of all of your disease. You would need to take into account a number of factors:

- Has the cancer already spread outside the prostate?
- How aggressive does the disease look (ie, what is the Gleason grade)?
- If surgery was used, was all of the cancer taken out?

Are some of these factors more important than others? Or do they all tell us the same thing?

Nomograms are simplified charts that have been specially constructed to weigh each of the necessary contributing factors and to provide a single assessment of the likelihood of remaining disease-free after treatment. The physician enters the relevant details from the case, and each factor is assigned a point value depending on how much it has been shown to contribute to the overall outcome.

A preoperative nomogram predicting the five-year recurrence-free probability



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For example, if a man’s PSA at diagnosis was 2 ng/mL, he might get 30 points, but if his PSA at diagnosis was 30 ng/mL, he might get 80 points. Why? Because, as we noted earlier, a higher PSA at diagnosis indicates that the disease has likely spread further, so that factor will contribute more to his overall outcome.

Once all of the points for the various factors are added, the nomogram shows us the chances that the disease will show up again five years after initial treatment. This is referred to as the *five-year recurrence rate*.

Let's look at the two extremes. If the total score were 140, the chart would show a five-year recurrence-free probability of 0.05 or 5%, meaning that 5 men out of every 100 with a score of 140 will be free of disease in five years. On the opposite end of the spectrum, a total

score of 20 would correspond with a five-year recurrence-free probability of 0.93 or 93%, meaning that 93 of every 100 men with a score of 20 will have no disease present at five years after initial treatment. Knowing how likely it is that you'll be disease-free in five years can be reassuring, especially if you're in

Nomograms are simplified charts that weigh a number of contributing factors and provide a single assessment of the likelihood of remaining disease-free after treatment.

the 20-point range. However, if you have *any* factors that indicate your tumor is aggressive, you might have a continued risk of recurrence even beyond the five years.

It is important to note that nomograms designed to predict the likelihood of recurrence are not predicting death from prostate cancer — a man can live for many years despite a recurrence. But they can play an important role in helping to decide whether to undergo additional treatments or whether to enroll in clinical trials assessing new therapeutic regimens or agents.

The Role of PSA Velocity

One of the benefits of nomograms is that they allow doctors to take into account a number of different factors, including PSA and Gleason score, that might contribute to your outcomes. But what we've been finding over the past few years is that certain factors can help predict outcomes by themselves, regardless of any other factors. For example, researchers have been looking more closely at how fast PSA rises, or the *PSA velocity*, and have noticed that in some men, the PSA rises rapidly, while in others, it rises slowly.

After looking at PSA velocity in a few hundred men, researchers

found something incredibly interesting: men whose PSA rose by more than 2.0 ng/mL per year before undergoing surgery or radiation therapy tended to have worse outcomes overall. They were more likely to have disease that had already spread, more likely to die from prostate cancer, and even more likely to die from other diseases.

That doesn't mean that men with rapidly rising PSA values will die from prostate cancer, or that their cancers will progress to advanced stages immediately. It also doesn't mean that we should ignore all other factors and use only PSA velocity to predict prognosis. What this does mean is that men who fall into this category need to follow up more regularly with their doctors.

The Team Approach to Prostate Cancer Care

A study published just a few years ago showed that urologists and radiation oncologists largely agree that the different treatment options for localized prostate cancer are probably equally effective. Nevertheless, assuming that you are a viable candidate for either approach, each group of specialists would still recommend the treatment option that he or she can provide — urologists would recommend surgery and radiation oncologists would recommend radiation.

The lesson to be learned from this study is not that doctors can't be trusted, or that they're more invested in their own best interests than in yours. The real lesson to be learned from this study is that prostate cancer specialists understand the ins and outs of their own field best of all, and are far more comfortable recommending therapies in that arena than outside of that arena. They therefore have an obligation to present to you the best information that they can deliver based on the knowledge that they have.

You have an obligation to yourself seek knowledge from all sources before making any treatment decisions. This is why it is important that you surround yourself with a team of physicians to discuss the different options. Talk with a urologist about surgical options; talk with a radiation oncologist about radiation options; talk with a medical oncologist about drug therapy options; talk with all of them about whether enrolling in a clinical trial might be a good choice for you. Most importantly, be sure that each doctor you see

has access to your complete medical record, including biopsy, ultrasound, CT, and/or MRI reports.

During the course of your disease treatment, you might receive several different types of treatments over a long period of time.

It is important that you keep all of your doctors informed about your progress and about what treatments you are getting, and that they communicate regularly with you and with each other to ensure that you're receiving the best care possible.

You have an obligation to yourself seek knowledge from all sources before making any treatment decisions.

In many of the larger cancer centers across the country, multidisciplinary teams of physicians work together on a regular basis. But even if you don't have access to those teams, there's no reason you can't build your own. Together, you and your multidisciplinary team of physicians will be able to decide on a treatment course that's right for you.

CHAPTER 2

Initial Treatment: Weighing the Pros and Cons of Each Option

There are three very different types of initial treatments for localized prostate cancer — active surveillance, surgery, and radiation therapy. Surgery and radiation therapy have both shown positive outcomes as front-line treatment. Either form of treatment can result in “cure” (defined as being disease-free for five years) in over 90% of men with localized prostate cancer.

Do you need to begin treatment right now or are you a candidate for active surveillance? As we’ll discuss in this Chapter, each of the different options requires a careful understanding not only of prostate cancer, but also of the way that you want to approach treatment. Your first step in deciding how to proceed must be to understand what each of the options actually accomplishes.

Initial treatment with surgery or radiation can result in “cure” in over 90% of men with localized prostate cancer.

Active Surveillance

We know that some prostate cancers grow more slowly than others, and that, some men are less likely to get sick and/or die from their cancers. If the treatments were easy and had few side effects, the unnecessary treatment of slow-growing cancers would clearly be outweighed by the benefits that appropriate treatment would bring. But, as we’ll discuss in more detail later, the available treatments for prostate cancer are serious, and can have a long-lasting effect on how you live your life. Consequently, determining *when* to initiate treatment can be one of the most difficult decisions to make.

The concept of active surveillance, or watchful waiting, has increasingly emerged in the past years as a viable option for men who, for one reason or another, have decided not to undergo immediate surgery or radiation therapy. Although some might say that



active surveillance is just postponing treatment, the truth is that for men who have very slow growing or very early cancers, immediate treatment might not make sense. Instead, they might choose to undergo vigilant monitoring, with frequent PSA and DRE tests. Additionally the use of ultrasound, CT, bone scans, or MRI might be used to watch for disease growth and the need for treatment. Active

Active surveillance has emerged in the past years as a viable option for men who have decided not to undergo immediate surgery or radiation therapy.

surveillance might also be a good choice for men who have other serious medical conditions that affect the way they live their lives, especially if these other conditions are likely to shorten their lifespan.

Are you a good candidate for active surveillance? That, of course, can only be determined after full consultation with your

doctors. Two recent studies evaluating this question have found that men who are older than age 65 as well as those who have low-grade tumors at diagnosis might do well with this approach. Put more bluntly, these men are likely to have fewer symptoms related to their disease and are more likely to die *with* prostate cancer than die *of* prostate cancer.

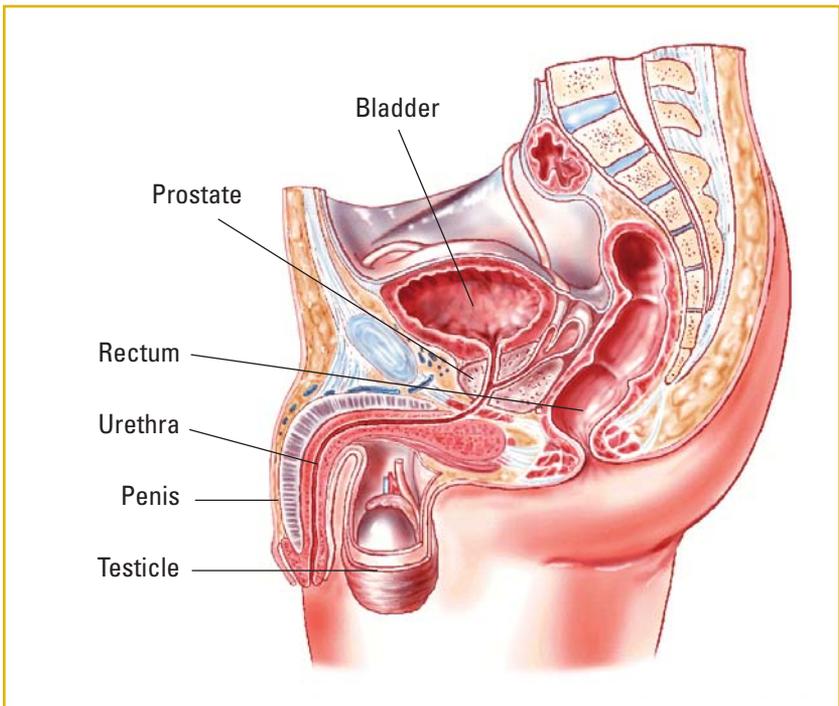
Another important factor that your doctors are likely to consider is how healthy you are overall. Many of the treatment options for prostate cancer can be difficult to endure, and the healthier you are going into treatment, the more likely you are to have better outcomes. If you're currently battling other disorders or diseases, such as heart disease, long-standing high blood pressure, or poorly controlled diabetes, your doctors might feel that it is in your best interest to hold off on therapy and avoid its potential complications.

When it comes down to it, every man's circumstances are unique, and there's no magic formula to knowing whether active surveillance is right for you. If you talk with your doctors and carefully weigh the pros and cons of the different treatment options before coming to any decision, you should be able to feel confident that the choice that you make is right for you.

A Lesson in Anatomy and Physiology

Before we move on to the details of surgery and radiation therapy, you will need to understand where the prostate is, what it does, and what surrounds it in the body. Not only will this help you better understand how each of the different procedures attempts to accomplish its goals, it will also help you understand why surgeons and radiation oncologists have been spending so much time perfecting their crafts, with a look toward maximizing treatment benefit while minimizing side effects.

Basic male genitourinary anatomy



The prostate is a small, squishy gland about the size of a walnut that sits under the bladder and in front of the rectum. The urethra, the narrow tube that runs the length of the penis and that carries both urine and semen out of the body, runs directly through the prostate.

After the kidneys filter out waste products from the blood, the

resultant urine is stored in the bladder. Under normal circumstances, the urinary sphincters, bands of muscle tissue at the base of the bladder and at the base of the prostate, remain tightly shut until they are relaxed during urination. During prostatectomy, after the prostate is removed, the bladder is pulled downward and is connected to the urethra at the point where the prostate had sat. If the sphincter at the base of the bladder is damaged during this process, or if it is damaged during radiation therapy, some measure of urinary incontinence or leakage will occur.

Sitting just above the prostate are the seminal vesicles, two little glands that secrete about 60% of the substances that makes up semen. It is estimated that about 10% of men have what is known as seminal vesicle invasion, meaning that the prostate cancer has either spread into the seminal vesicles or has spread around them, so the vesicles are typically removed during prostatectomy and are targeted during radiation therapy. The loss of the prostate and the seminal vesicles renders men infertile.

Running alongside and attached to the sides of the prostate are the nerves that control erectile function. If these nerves are damaged, which was standard during prostatectomy up until the mid 1980s, the ability to achieve erection is lost. Sexual desire is not affected, but severing or otherwise damaging the nerves that stimulate the processes by which erection occurs leads to erectile dysfunction.

Finally, sitting just behind the prostate and the bladder is the rectum, the lower end of the bowel just above the anal sphincter. Solid waste that is filtered out of the body moves slowly down the intestines, and, under normal circumstances, the resultant stool is excreted through the anus following conscious relaxation of the sphincter. Damage to the rectum caused by radiation, or, more rarely, by surgery, can result in a number of bowel problems, including rectal bleeding, diarrhea, or urgency.

Radical Prostatectomy

The concept behind the surgical approach toward cancer treatment is simple: isolate the tumor and cut it out. Unfortunately, in practice, nothing is that simple.

“Prostate cancer” is really misleading; a better term would be

“prostate cancers.” Unlike breast cancer, which grows from a single tumor and spreads outward, prostate cancer is actually a number of small tumors scattered throughout the prostate. So cutting the tumor out of the prostate is not really an option. Instead, the entire prostate plus some surrounding tissue is removed, including the nearby seminal vesicles.

In the most common type of surgery, known as *radical retropubic prostatectomy*, an incision is made in the abdomen and the prostate is cut out from behind the pubic bone (hence the term *retropubic*, meaning behind the pubis, the front part of the pelvis). As we noted above, the urethra, the narrow tube that runs the length of the penis and that carries urine from the bladder out of the body, runs directly through the prostate on its way out of the bladder. Therefore, after removing the prostate, the surgeon must stitch the urethra directly to the bladder so urine is once again able to flow.

Note that because it typically takes a few days for the body to get used to this new setup, the surgeon will insert a *catheter*, or tube, into the bladder. With this in place, urine flows automatically out of the bladder, down the urethra, and into a collection bag without the need for conscious control of the sphincter. The catheter is usually kept in place for about a week to 10 days, after which the stitches have healed enough that the system should be able to work on its own. Because the average hospital stay is shorter than the average time that the catheter is left in the bladder, you’ll need to visit with your doctor or nurse to have the catheter removed.

Another type of surgery, known as *radical perineal prostatectomy*, is performed less frequently these days. In this approach, the surgeon makes the incision in the *perineum*, or the space between the scrotum and the anus, and the prostate is removed from behind. Although there is typically less blood loss with this approach, most surgeons find it harder to see the surrounding structures so the precision required to preserve both urinary and erectile function is more difficult to achieve.

The concept behind the surgical approach toward cancer treatment is simple: isolate the tumor and cut it out.

Nerve-Sparing Prostatectomy

A few new advances have come along in recent years that are designed to maximize benefits and to minimize side effects. By far, the most important one is the nerve-sparing technique. As we noted above, the nerves that control erectile function lie right alongside the prostate. If no care is given to sparing them, erectile function is almost always lost. The nerve-sparing technique was first pioneered in the 1980s, and has since been practiced and perfected by thousands of surgeons around the world. But that doesn't mean it's always done.

In order to spare the nerves, the surgeon has to carefully cut to the very edges of the prostate. This is an important issue because if there are any cancer cells beyond where the surgeon has cut, they can grow and spread, and you will not be cured. If your cancer has spread outside of the prostate, the surgeon will need to cut out more of the surrounding tissues and therefore likely won't be able to spare the nerves. Obviously, if this is known in advance, you will be able to take this into consideration when making your treatment choice. But sometimes the CT or MRI won't show that the cancer has spread, and the doctor will be forced to make the final decision after the operation has already begun.

In short, the decision on whether to *attempt* a nerve-sparing procedure should be yours — only you can know how important it is to maintain your erectile function. But ultimately the decision on whether to *perform* the nerve-sparing procedure is up to the surgeon based on his or her years of experience and expert clinical judgment. Remember that the goal of the surgery is to cure you of your disease. If the surgeon does not feel that he or she can cure you and leave the nerves intact, the nerves will not be spared.

Nerve Grafting

Nerves are like electrical wiring. Their function is to carry and deliver a spark, jolting the muscle cells into moving. If the nerve were to die, the muscle can't work because it's missing the jolt of electricity to get it started. In theory, just as electricians can replace faulty wiring, surgeons should be able to replace faulty nerves. In practice, of course, it's never that simple.

As we discussed earlier, the nerves that control erectile function run alongside the prostate. If the surgeon feels, for whatever reason,

that the nerves cannot be spared during surgery, erectile function is lost. However, a number of years ago, surgeons started looking at the possibility of removing nerves from other locations in the body (most often from the side of the foot) and surgically attaching, or grafting, them to the ends of the cut nerves. About 30% of men undergoing this procedure report natural erections after about six months, and up to 50% achieve erections with the assistance of oral medications.

Note that because of the technical skill required to perform the procedure, nerve grafting is not widely practiced. In addition, men undergoing this procedure will be in surgery for a longer period of time and will have a second surgical incision at the point from where the nerve was taken, potentially increasing the chances for postsurgical complications. Therefore, a nerve-sparing prostatectomy should be the first choice; nerve grafting should be seen only as a potential option if the surgeon feels it is appropriate.

Laparoscopic Surgery

In the typical retropubic prostatectomy, a vertical incision about 4 inches long is made in the abdomen. The wide opening allows the surgeon to see all of the internal organs as well as the surrounding blood vessels and nerves. But in the 1990s, surgeons started applying to prostatectomy the same surgical technique that had been used in the more “minor” surgeries such as removal of the appendix or gallbladder.

In *laparoscopic* surgery, four or five very small incisions — about a half inch each — are made in the abdomen. Through each incision, the surgeon inserts a narrow instrument with tiny cameras and/or surgical tools attached to the end, allowing the surgeon to visualize and operate on the internal structures without cutting open the entire abdomen. Further refinements on this technique led to the development of a robotic interface, where the surgeon maneuvers the robot’s arms, which in turn control the cameras and instruments inserted in the abdomen — effectively performing the operation via remote control.

The benefits of laparoscopic surgery are obvious: smaller incisions and less invasive surgery leads to less blood loss and shorter hospital stays. However, because this type of procedure is far more challenging than the standard “open” prostatectomy, and the learn-

ing curve for becoming proficient is steeper, surgical skill becomes even more important.

If laparoscopic surgery is performed by an experienced, well-qualified surgeon, the outcomes can be as good as traditional open surgery, and, in some cases, even better because it is less invasive. But if you don't feel comfortable with the procedure, remember that the decision about whether to undergo laparoscopic surgery with or without robotic assistance vs traditional surgery is yours and yours alone.

The Importance of Surgical Skill

In every area of life, we recognize that some people are simply better at performing some jobs than others, whether due to experience or natural talent. The same is true for doctors and surgeons. Yes, there are established techniques and standards that any competent surgeon

should be able to follow. And there's absolutely no guarantee that even if you were to go to the best surgeon in the world who has performed hundreds of operations, you'll fare any better than if you went to someone who's performed just a handful. Prostatectomy, like many surgical procedures, is very delicate

Your surgeon should have enough experience to not only perform the operation but to also make an informed clinical judgment and change course should the need arise.

work, and the difference between a good surgeon and a great surgeon can affect outcomes. At a minimum, you should ensure that the surgeon you choose is someone in whom you have confidence, and someone who has enough experience to not only perform the operation, but to also make an informed clinical judgment and change course should the need arise.

Radiation Therapy

Unlike prostatectomy, which uses surgery to remove the disease entirely from the body, the goal of radiation therapy is to kill the prostate cancer cells where they live. To accomplish this, very high doses of x-rays are delivered to the prostate, concentrated on the

small clusters of tumor cells that comprise the cancer within the prostate gland.

The most common type of radiation therapy is *external beam radiotherapy*. Radiation oncologists and technicians use CT scans and MRIs to map out the location of the tumor cells, and x-rays are targeted to those areas. With *3-D conformal radiotherapy*, a computerized program maps out the exact location of the prostate tumors so that the highest dose of radiation can reach the cancer cells within the gland. Because the treatment planning with this type of radiation therapy is far more precise, higher — and more effective — doses can be used with less chance of damaging surrounding tissue.

Intensity-modulated radiation therapy (IMRT) takes the dose planning one step further. Studies have clearly shown that delivery of higher doses of radiation results in better outcomes. However, if you remember from the anatomy lesson above, the prostate lies right next to two rather important internal structures: the bladder and the rectum. Radiation damage to either of those organs can result in significant urinary and bowel problems that are not only unlikely to improve over time, but that have been shown to worsen over time as the effects of the radiation accumulate. To avoid these problems, oncologists might be tempted to opt for delivering lower doses of radiation — at the expense of decreasing the chances for cure.

IMRT does exactly as its name suggests — it allows oncologists to modulate, or change, the intensity of the doses and radiation beams to better target the radiation delivered to the prostate, while at the same time delivering lower doses to the tumor cells that are immediately adjacent to the bladder and rectal tissue. With this approach, the local side effect rate is lowered further while keeping the cure rates as high as possible.

Regardless of the form of external radiation therapy, treatment courses usually run five days a week for about seven or eight weeks, and are typically done on an outpatient basis.

Brachytherapy

The goal of brachytherapy, or seed implantation, is the same as that of external radiation therapy: to kill the prostate cancer cells where they live. The difference, however, is that brachytherapy does it from

within the prostate itself and external radiation therapy does it using beams directed into the prostate from the outside.

With this approach, tiny little metal pellets containing radioactive iodine or palladium, each smaller than a grain of rice, are inserted into the prostate via needles that enter through the skin behind the testicles. As with 3D conformal radiation therapy, careful and precise maps are used to ensure that the seeds are placed in the proper locations. Over the course of several months, the seeds give off radiation to the immediate surrounding area, killing the prostate cancer cells. By the end of the year, the radioactive material degrades, and the seeds that remains are harmless.

Compared with external radiation therapy, brachytherapy is still less commonly used, but it is rapidly gaining ground — primarily because it doesn't require daily visits to the treatment center.

A twist on brachytherapy, known as *high-dose-rate brachytherapy*, does for brachytherapy what IMRT does for external radiation therapy: it allows radiation oncologists to deliver very high doses of radiation to very specific areas of the prostate while sparing other areas and minimizing side effects. Unlike IMRT, however, the advantages of the high-dose-rate brachytherapy approach are not so clear.

Technical skill and manual dexterity can play an important role in determining outcomes from radiation therapy.

Instead of surgically implanting the seeds and leaving them in the prostate permanently, the high-dose-rate technique involves inserting hollow tubes into the prostate through which high doses of radioactive iridium are delivered

to carefully mapped out locations in the prostate. The tubes, however, are not designed to stay in the prostate permanently. Rather, they are left in place for two to three days, and each day another dose of the iridium is delivered. After the final dose, the tubes are removed. This procedure is done on an inpatient basis, rather than an outpatient basis, and is typically followed by a short course of external radiation therapy. Because of the relative inconveniences of this technique over standard brachytherapy, high-dose-rate “temporary” brachytherapy hasn't quite caught on as a standard treatment approach, and its use remains somewhat more limited.

The Importance of Dose Planning

Just as surgical skill can play an important role in determining outcomes from prostatectomy, technical skill and manual dexterity can play an important role in determining outcomes from radiation therapy. Because the prostate cancer is surrounded so closely by other internal organs, a decision to use an x-ray beam even a millimeter or two to one side or another can result in damage to healthy tissue. The use of computer software to assist with the dose planning and target prostate tissue helps greatly, but, in the end, the skill and experience of the radiation oncologist will make the biggest difference. At a minimum, you should look for a radiation oncologist who has broad experience with an assortment of approaches and who can objectively help you decide which approach might be right for you.

Neoadjuvant Hormone Therapy

As we'll discuss in Chapter 6, hormone therapy remains a staple in the management of advanced prostate cancer. But in the past few years, researchers have been exploring ways to incorporate this therapy earlier, in the hopes of improving outcomes even more.

Hormone therapy is the general term given for any surgical or drug therapy that prevents the release and/or action of testosterone, the naturally occurring male hormone that fuels prostate cancer growth. A number of studies have shown that initiation of short courses of hormone therapy can shrink larger tumors, thereby making it easier for oncologists to localize the radiation needed to kill the tumor cells, and significantly improving outcomes. This use of *neoadjuvant* hormone therapy (*neo*, meaning first or early; *adjuvant*, meaning in addition to) is separate and distinct from the hormone therapy that you might receive should your prostate cancer return.

The boost that neoadjuvant hormone therapy gives to the success of radiation therapy has resulted in the approach becoming the stan-

Because of the boost that neoadjuvant hormone therapy gives to radiation therapy, the approach is now used in many institutions for men with high-grade or bulky cancers.

standard of care in many institutions for men with high-grade cancers and/or those with larger, bulkier tumors.

Other Approaches: Cryotherapy, High-Intensity Focused Ultrasound, and Primary Hormone Therapy

Surgery and radiation therapy remain the standard treatment for localized prostate cancer, but that doesn't mean that other, less popular treatment options might not be right for you.

Cryotherapy, also known as cryosurgery or cryoablation, has been around for years, but until a few years ago, it was rarely used. With this approach, probes are inserted into the prostate through the perineum (the space between the scrotum and the anus), and argon gas or liquid nitrogen is delivered to the prostate, literally freezing to death the prostate cells and any prostate tumors. Over the years, a number of modifications were made to avoid freezing damage to the nearby structures, but the rates for both erectile and urinary dysfunction remain high, and data on long-term outcomes are limited.

High-intensity focused ultrasound works in exactly the opposite way: the prostate cells are heated to death. A probe is inserted into the rectum, from which very high-intensity ultrasound waves are delivered to the target area. Although this technique remains experimental in the United States, it's been used in Europe for a number of years with a fair amount of success.

Hormone therapy is a drug treatment designed to suppress the release and/or action of testosterone. As we'll see in Chapter 6, because testosterone is known to fuel prostate cancer cell growth, blocking it is a commonly used strategy in men whose cancers are either not cured by local therapy or whose cancers are diagnosed at a stage when local therapy cannot be performed.

Although there is little, if any, data to show that hormone therapy alone is an effective treatment strategy for men with localized prostate cancer, it is increasingly being used in this setting. Because it is not invasive, it is possible that the therapy is seen as a middle ground between active surveillance and local therapy.

As time goes on and the benefits of these treatment options are further explored, it's possible that they will move more into the

mainstream. For now, though, none are seen as standard treatments for localized prostate cancer.

Deciding on a Course of Therapy

Now that we've reviewed the ins and outs of the different types of therapies, how do you know which is the right one to choose?

For most men, the decision will rest on a combination of clinical and psychological factors. Men diagnosed with localized prostate cancer today will likely live for many years, so any decision that is made now will likely reverberate for a long time. Careful consideration of the different options is an important first step in deciding on a treatment course that's right for you.

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Tailoring Treatment to Your Disease

There are three clinical factors that doctors will look at in determining whether surgery or radiation therapy might be the right course.

The most significant clinical factor that might sway your decision one way or another is the extent of your tumor. If your cancer has spread beyond the capsule, or outermost layer, of the prostate, surgery might not be the best choice for you. In fact, for some surgeons, this factor alone would cause them to counsel you away from this treatment approach. However, this requires that the surgeon would know in advance exactly where the tumor ends and where the healthy tissue begins. As we noted earlier, because this is not always possible, it is imperative that if you choose surgery, you choose a surgeon whom you trust can make a well-educated decision to alter the original plan should it prove necessary.

On the other hand, tumors that are confined to the prostate are also excellent candidates for radiation therapy. The radiation oncologist will have an easier time planning out the doses, and the likelihood of damage to the surrounding organs is very small. But

remember that accurate dose planning is crucial to good outcomes. Be sure to choose a radiation oncologist who has considerable experience in the type of treatment you select.

If the extent of the tumor turns out not to be the deciding factor, overall health might be. Prostatectomy, even if done laparoscopically, is major surgery. Heart disease, breathing difficulties such as asthma or emphysema, and blood clotting problems can all be factors that work against you when deciding whether surgery is appropriate. Be sure your doctors know about all of your health problems so they can help you can make the most well-informed decision possible.

For radiation therapy, your overall health status is typically less of an issue. The x-rays are so focused on the prostate that there are few, if any, effects seen outside of the local area. Fatigue, however, is common as treatment progresses, especially if higher doses are used to better kill the cancer cells. Plan to keep a lighter schedule during your course of radiation, and allow for some additional relaxation or nap time each treatment day.

The third clinical factor is age. Traditionally, it was assumed that younger men fared better with surgery and older men fared better with radiation therapy. Today, few doctors take such a polarizing viewpoint on age. Instead, they use age as a surrogate for longevity: if you have a life expectancy of less than 10 years, surgery is probably not the best option, and radiation therapy might be a better choice.

The reasoning behind this approach is somewhat complicated. Partly it relates to overall health, because it is assumed that older men will have other illnesses that will make them less than ideal candidates for surgery. And partly it relates to a general sense that people who have limited years ahead of them shouldn't have to undergo the long recovery from surgery if a less onerous treatment strategy is available. For many doctors, men who are above age 75 will likely be counseled away from prostatectomy and toward radiation therapy or active surveillance.

Psychological Factors

It's important to remember that the decision about how to treat your prostate cancer can't be made in a vacuum. So many aspects of this disease can affect the way you view yourself, the way you interact with others, and the way others interact with you. The final decision on

whether to choose surgery or radiation therapy might therefore be more tied to a weighing of the psychological, rather than the clinical, factors that are tied up with your prostate cancer.

The first issue to consider is your attitude toward your disease. Although all men see their prostate cancer as something that they want to eradicate, there are generally two ways of looking at how that should be done: cut it out with surgery or kill it with radiation therapy. Your viewpoint on this issue can play an important role in determining how you want to approach your treatment choice. On the other hand, if you have less aggressive prostate cancer but have other medical concerns that need your attention now, active surveillance might be the right choice.

The second issue to consider is the potential side effects of the treatment. (For some men, this issue will be the *only* one that matters.) In the hands of a skilled surgeon, men who undergo a nerve-sparing prostatectomy will likely regain erectile and urinary function within a few months; in the hands of a skilled radiation oncologist, men who undergo radiation therapy will see few bladder or bowel problems. But if your tumor is not as well confined as we would hope, complications can arise. Only you can know which set of potential side effects are more important, and which set will make you decide on one or another course of therapy.

Remember: If, due to illness or other reasons, you already have difficulty achieving an erection or maintaining bladder or bowel control, the best that you can expect to see after treatment is a return to where you started.

Taking the Plunge and Making the Decision

In the end, after all of your research into the different treatment types, different doctors, and different hospitals, the decision is going to come down to your gut: in your heart of hearts you have to *know* that your choice is right for you. It might not be right for your brother or your friend, and it might not be right for the twenty other people that you spoke with to get some more opinions. But you need to know that it's right for you so you can get started on the road toward leading a healthier — and cancer-free — life.

CHAPTER 3

Maximizing Quality of Life After Initial Treatment

Many men understand that when the prostate cancer is caught early, it can be curable, and that the primary treatment options for localized disease are all excellent choices. However, many men also have significant concerns about the side effects of these treatments. While there is ample justification for these concerns, there are also many misunderstandings about the actual frequency of these side effects, their severity, and what can be done to counteract the occurrence or the management of treatment side effects.

Many of the side effects that men fear most following local treatment are oftentimes less frequent and severe than you might think. As

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we've already noted, technical advances in both surgery and radiation therapy have vastly improved outcomes, and, as we'll discuss here, researchers have been working hard to find ways that can help to overcome some of these side effects as well.

In this Chapter, we'll review the statistics to see how often these side effects really occur, and look at some of the ways you might be able to work with your doctor to minimize how these side effects, if they occur, will affect your daily life.

Urinary Dysfunction

The broad term of urinary dysfunction encompasses many different urinary problems. The most common definition is urinary incontinence, which can range from some leaking to complete loss of bladder control. But there are also more subtle changes that can significantly affect your daily life. These changes, which are collectively known as irritative voiding symptoms or urinary bother, include increased urinary frequency, increased urinary urgency, and pain upon urination.



For men undergoing prostatectomy, incontinence is the primary urinary side effect. Surgical technique plays an important role in determining outcomes; as we discussed earlier, carefully dissecting out the tumor without affecting the urinary sphincter is key. But presurgical urinary function can play an important role as well. If you've already experienced some hesitation and/or lack of bladder control, it will be harder for you to regain full control and function.

On average, about 25% of men report frequent leakage or no control and a need to use absorbent pads at six months after treatment; by two years, fewer than 10% report using pads at all. Keep in mind, however, that the definition of incontinence is very subjective, and the degree of incontinence you will experience cannot be determined before you undergo treatment.

External beam radiotherapy can irritate both the bladder and the urethra, causing inflammation or swelling of the prostate. Most of the symptoms lessen over time with little or no intervention: nearly 45% of men report irritative voiding symptoms after six months, and the majority resolve by one year. However, the symptoms can persist in some men, with about 10% of men still requiring medication after two years. Urinary dysfunction following brachytherapy tends to be more severe initially because of the increased trauma to the prostate after implantation of the radioactive seeds. Over 70% of men have symptoms requiring medication within six months after seed implantation, but the rate drops to 25% or less after two years.

Some men might experience spontaneous bleeding into the urine on occasion in the years after radiation. This is because a late effect of the radiation is to cause the blood vessels in the lining of the bladder to weaken and become fragile. If bleeding occurs, it is common for the urologist to check inside the bladder just to make sure that there is not a more important and serious cause of the bleeding other than past radiation therapy. The condition usually stops by itself, but occasionally the urologist might need to perform a minor procedure to close off any troublesome bleeding points.

Urinary symptoms from initial therapy typically lessen over time, and return to baseline in the majority of men within one year.

Treatment Options

Because the urinary symptoms following radiation therapy are irritative in nature, drugs that improve urinary flow are commonly used. Tamsulosin (Flomax), terazosin (Hytrin), and other alpha-blockers are typically instituted in all men following radiation therapy for at least a few weeks, and are gradually withdrawn as symptoms improve. Note that the oral medications for erectile dysfunction can interact with these drugs, so be sure that your doctors know which drugs you're taking.

In severe cases, insertion of a catheter or a surgical procedure to remove part of the swollen prostate might be necessary, but improvements in dose planning tend to lessen the possibility of this occurring. As with surgery-related urinary side effects, practitioner skill can play an important role in determining severity and duration of symptoms following any form of radiation therapy.

In cases of persistent urinary incontinence, the least invasive procedure is designed to make the sphincter's job a bit easier. By injecting collagen into the urethra, the passageway tightens, making it more difficult for urine to leak through. Although over 50% of men stay dry with this procedure, the effects only last for a short time, so it's not really a permanent solution to the problem.

Longer lasting results are seen with surgical procedures. The simplest procedure is a takeoff on a commonly used procedure in women with incontinence and is based on the theory that the damaged sphincter is not strong enough to withstand abdominal pressure — the pressure builds up, the sphincter gives up, and urine leaks out. A sling made from silicone or, more rarely, human tissue is slipped under the urethra and anchored to the muscle or bone, relieving the urethra from pressure buildup in the abdomen as urine accumulates in the bladder. The sling results in urinary function improvements in about 70% of men after prostatectomy, although only about half of those reported being completely dry after four years. Following radiation therapy, only 30% of men showed an improvement, with even fewer men reporting being completely dry after four years.

The most common complication of the sling placement is a need for tightening of the bolsters that hold it in place, requiring a second surgery. Infection and erosion of the sling can also occur, both of which can also require surgical intervention. Nevertheless, this pro-

cedure can be very useful in men who are persistently incontinent after prostatectomy.

About 5% of men who undergo prostatectomy will respond to none of the therapies described above and will remain incontinent. In these men, surgical placement of an artificial sphincter remains the treatment of choice. A cuff is placed around the urethra, and a release button is implanted in the testicle. Until the button is pressed, the cuff remains tight around the urethra and prevents urine from leaking through. Once the button is pressed, the cuff loosens and the urine flows.

Nearly all men who undergo this procedure see some improvement, but only about half remain completely dry and continue to need one or two pads a day. Complications can occur, and surgical revision is sometimes necessary. Yet despite all of this, and despite the fact that it's an unnatural way to urinate, the vast majority of men who undergo the procedure find that it satisfactorily resolves their need for urinary control.

Bowel Dysfunction

The broad term of bowel dysfunction includes diarrhea or frequent stools; fecal incontinence or the inability to control bowel movements; and rectal bleeding. By far, all of these side effects are more common following external beam radiotherapy than any other primary therapy, but as techniques and dose planning strategies improve, even these rates have been dropping.

If you recall from the anatomy lesson in Chapter 2, the prostate presses up against the rectal wall. During prostatectomy, damage to the rectum is rare, and the bowel changes seen in the first few weeks following surgery are more likely the result of the body adjusting to the increased abdominal space with the loss of the prostate. Radiation therapy, however, can cause significant damage to the rectum, resulting in any and all of the symptoms listed above.

Standard external beam radiotherapy blankets a wide area with radiation. Not surprisingly, the highest rates of bowel dysfunction are seen with this type of therapy. In addition, bowel function tends to remain the same or deteriorate rather than improve over time as the effects of radiation accumulate. After two years, about 10% of

men reported having persistent diarrhea a few times each week, while rectal bleeding increased steadily from 5% immediately after treatment to 25% after two years.

Rates with 3-D conformal radiation therapy are considerably lower, but they, too, increase over time, and, after two years, are similar to those seen with standard external beam radiotherapy. By contrast, after two years, the rates with intensity-modulated radiation therapy (IMRT) remain low, hovering around 5%. Bowel dysfunction following brachytherapy tends to be lower than that seen with external beam radiotherapy, and, most importantly, seems to stabilize at a low rate after just one year. (See Chapter 2 for more detailed information about radiation therapy for initial treatment.)

As techniques improve and dose planning becomes more sophisticated, it's likely that the rates of long-term bowel side effects will go even lower. In the meantime, as with all other side effects, much depends on practitioner skill, so be sure to select a doctor who pos-

sesses the experience and skill to spare the rectal tissue as much as possible.

Short of treating the individual symptoms as needed, there are few, if any, treatment options for bowel dysfunction following radiation therapy. Careful monitoring of the diet

As radiation therapy techniques improve and dose planning becomes more sophisticated, it's likely that the rates of long-term bowel side effects will go even lower.

to avoid foods that might irritate the gastrointestinal tract is important, but complete elimination of fibrous, bulky foods can lead to constipation and straining, which in turn can exacerbate rectal bleeding. Working with your doctors and nurses as well as with a nutritionist can help you identify which foods might help promote bowel healing while minimizing irritation and further problems.

Erectile Dysfunction

In various studies reported in the medical literature, you will find an extraordinarily wide range of erectile dysfunction rates — ranging from a low of 2% to a high of 98%. But if you look more carefully at what these studies measured, a few things stand out.

The first issue to consider is the procedure being studied. For example, when looking at men undergoing prostatectomy, you need to distinguish between those who underwent nerve-sparing procedures and those who didn't. If the nerves are cut or otherwise damaged during surgery, it is highly unlikely that any spontaneous erections will occur. Remember, too, that the nerve-sparing procedure became more widely used relatively recently. So unless they were treated at a major cancer center with a rigorous prostate cancer program, men who underwent prostatectomy 10 or more years ago are unlikely to have had a nerve-sparing procedure. Be sure to keep that in mind when discussing treatment options and side effect profiles with other men with prostate cancer. The same is true with radiation therapy. Brachytherapy and IMRT deliver much more focused radiation to the prostate tissue and therefore cause less damage to the surrounding tissue. The side effect profile for these procedures can vary compared with the side effects seen with standard external beam radiotherapy.

The second consideration is how one actually defines erectile dysfunction. Is it referring strictly to spontaneous erections? What if medication or mechanical devices are used? The technical definition of a "normal" erection is one that stays rigid sufficient for sexual intercourse. But it's often difficult to distinguish between technical erectile function and subjective sexual function, which will obviously vary much more widely from person to person.

Finally, the third consideration is the time factor. Erectile function rates tend to improve over time following prostatectomy, but tend to remain stable following radiation therapy or decline over time. Therefore, identifying how long it's been since treatment is an important part of understanding how erectile dysfunction might affect your life.

Given these three caveats, let's look at the numbers.

Regardless of whether the nerves were spared during surgery or whether the most precise dose planning was used during radiation therapy, nearly all men will experience some erectile dysfunction for the first few months after treatment. The reason for this is simple: the nerves and blood vessels that control the physical aspect of an erection are incredibly delicate, and any trauma to the area will result in changes to the natural order. However, within one year after treat-

ment, nearly all men with intact nerves will see a substantial improvement. By this point, about 50% of men who undergo nerve-sparing prostatectomy will have returned to their pre-treatment function; after two years, about 75% will have returned to pre-treatment function. (Remember, you can only get back to where you started.) For those who underwent radiation therapy, the numbers are better, but tend not to improve too much over time. About 25% of men who undergo brachytherapy will experience erectile dysfunction vs nearly 50% men who have standard external beam radiation; after two years, few men will see much of an improvement.

Of course, the challenge lies in trying to figure out how you will fare compared with the averages. The two most important factors in anticipating whether a man will regain erectile function following

treatment are the type of procedure (coupled with practitioner skill) and prior sexual function. Men who undergo procedures that are not designed to minimize side effects and/or those whose treatments are administered by physicians who are not proficient in the procedures will

If restoring erectile function after initial therapy is important to you, be sure to fully investigate the success rates of your doctors before you begin treatment.

fare worse. If restoring erectile function after initial therapy is important to you, be sure to fully investigate the exact type of procedure and the success rates of the individual surgeon before you begin treatment.

But it is equally important to be realistic about what to expect after treatment. If you have other diseases and/or disorders that have impaired your ability to maintain an erection, you'll have a more difficult time returning to pre-treatment function. Diabetes, vascular problems, smoking, and even certain drugs are known to cause sexual side effects — add in the possible trauma to the genital region during treatment and it's not too surprising that it can take a while, even a few years, for things to get back on track.

Oral Medications

In 1998, a remarkable new medication came on the market. Known as sildenafil (Viagra), the drug was the first oral medication approved

by the FDA to treat erectile dysfunction. When a man is sexually stimulated, sildenafil, along with two similar drugs released a few years later, tadalafil (Cialis) and vardenafil (Levitra), relaxes the muscles in the penis, allowing blood to rapidly flow in. As with a natural erection, tiny valves at the base of penis lock shut, preventing the blood from flowing back out and therefore causing the penis to stay rigid. On average, the drugs take about an hour to begin working; the erection-helping effects of sildenafil and vardenafil last for about 8 hours and tadalafil about 36 hours. About 75% of men who undergo nerve-sparing prostatectomy or more precise forms of radiation therapy have reported successfully achieving erections after using these drugs.

However, these drugs are not for everyone. Many men with angina or other heart problems take medications that contain nitrates to help the blood flow better to the heart. All three agents used for erectile dysfunction can affect the way that the nitrates work — and cause your blood pressure to drop to dangerously low levels. They can also interfere with alpha-blockers, drugs that are commonly used in men with the noncancerous growth of the prostate known as BPH, and that are often used in men following certain types of radiotherapy, particularly brachytherapy. It's important therefore to make sure that all of your doctors know about any and all medications that you might be taking.

Interestingly, recent data have shown that the oral drugs for erectile dysfunction might have a role in speeding up the recovery process after primary therapy. As we noted earlier, even if the nerves are not irreparably damaged during surgery or radiation therapy, it can take up to a year for full erectile function to return. Nevertheless, many men have found that daily use of the oral drugs can help to “rehabilitate” their erectile function and return them to baseline function more quickly. Although this use has become rather common in many centers across the country, clinical studies are just now underway to determine the optimal usage and dosage, so be sure to discuss with your doctor whether this approach is right for you before attempting any sort of therapeutic use of these drugs on your own.

Finally, remember that these are not recreational drugs; they're very serious medications. Don't attempt to buy cheaper versions of the pills on the Internet that might or might not contain the medication that you need.

Injections, Mechanical Devices, and More

If the oral medications don't work, or if you can't take them because you have other health issues, there are a number of alternative treatments that might be helpful. Because they require a bit more work than taking an oral medication, they're not typically seen as the first option. But if you do need to use one of these treatments, remember for all of the years before 1998, these were the only options available, so you're not alone.

As we noted above, the basic concept behind the oral medications is to allow blood flow into the penis so it can become rigid. This same approach is used by two other treatments as well.

MUSE is a medicated pellet about half the size of a grain of rice that is inserted into the urethra through the opening at the tip of the penis using a disposable plastic applicator. Unlike the oral medications, there is no need for sexual stimulation in order for it to work, but some manual stimulation and massage is required to help achieve rigidity. An erection typically occurs within 10 minutes after insertion of the pellet, and can last for 30 to 60 minutes. About 40% of men have reported successfully achieving erections after using this drug, but the results are often inconsistent. Some local reactions, particularly a burning sensation, are frequently seen, and many men discontinue use after a short time.

Caverject uses the same drug that is in the *MUSE* pellets, but delivers it via an injection directly into the penis. It, too, takes about 10 minutes to work and lasts for about 30 minutes. Although nearly 90% of men using *Caverject* reported erections about six months after therapy, as you can imagine, most men are not willing to inject themselves regularly, so the treatment is not often used for long periods of time.

The drug in both of these systems works in a similar fashion to the one in the oral medications, but the short-lived action and the local insertion or injection of the drug make it far less likely to affect the action of other medications. Nevertheless, it's always a good idea to make sure that each member of your care team has your complete medical history and a full listing of all medications that you might be taking.

For those unwilling or unable to use any form of medication to help improve erectile function, there are still a number of choices.

The most commonly used option is the vacuum constriction device, or vacuum pump. Remember, in order to achieve erection, you must have a rush of blood into the penis and no flow back out. The vacuum device accomplishes the same thing, only in a mechanical fashion. The penis is inserted into a plastic tube that is sealed at one end. The air is pumped out of the tube, causing blood to flow in and for the penis to become erect. However, because this is a mechanically driven erection, the blood starts to flow back out once the vacuum seal is broken. Therefore, a rubber ring is rolled onto the base of the penis, constricting it sufficiently so that the blood does not escape.

About 80% of men find this device successful, but it, too, has a high drop-out rate — partly because it's somewhat cumbersome to use, but mostly because the erections tend to feel somewhat unnatural. The constriction ring at the base of the penis is effectively cutting off fresh circulation. Because of this effect, it is crucial that the ring be removed immediately after intercourse, or the tissue can be damaged due to lack of flowing oxygen.

The final option for treating erectile dysfunction is the surgically inserted penile implant. There are a few different types of implants, but the one that provides the most natural feeling when erect and when non-erect is the three-piece prosthesis. A narrow flexible plastic tube is inserted along the length of the penis, a small balloon-like structure filled with fluid is attached to the abdominal wall, and a release button is inserted into the testicle. The penis remains flaccid until an erection is desired, at which point the release button is pressed and fluid from the balloon rushes into the plastic tube. As the tube straightens from being filled with the fluid, it pulls the penis up with it, creating an erection.

The surgical procedure is done under general anesthesia, so this option is not available to men who are not considered good candidates for surgery because of other health reasons. In addition, in a small percentage of cases, the device can malfunction, requiring a second surgery to repair it. Finally, because the penile tissue itself remains unchanged, the erection can seem somewhat unnatural. Nevertheless, assuming the mechanics are working correctly, it is, by definition, 100% effective, and about 70% of men remain satisfied with their implants even after 10 years.

Fertility

The loss of fertility after prostatectomy or radiation therapy might not be a side effect that comes to mind. However, the increasing rates of men being diagnosed with prostate cancer at younger ages coupled with the increasing rates of men fathering children at older ages makes fertility a growing area of concern.

Despite the best efforts of surgeons and radiation oncologists, it is nearly impossible for a man to retain his ability to father children through sexual intercourse after initial treatment. During prostatectomy, both the prostate and the nearby seminal vesicles are removed. The seminal vesicles are two small structures that lie at the base of the bladder. Together with the prostate, they provide semen that carries the sperm down the urethra and out the penis during ejaculation. The loss of semen following surgery makes ejaculation impossible, so the sperm cannot physically make it out of the body to reach the woman's egg for fertilization. Note that the loss of ejaculation does not mean a loss of orgasm; without semen, men experience what is known as a "dry orgasm" — reaching a climax, but not ejaculating, or, in rare cases, ejaculating a small amount of semen.

With radiation therapy, fertility is nearly always impaired. Radiated prostate cells and seminal vesicles tend to produce semen that cannot transport the sperm well. In addition, the sperm, which is made and housed in the testicles, can be damaged, but this is seen far less frequently with more accurate dose planning.

For men who wish to father children after treatment for prostate cancer, the best chance for fertility is sperm banking. Semen containing sperm is frozen in liquid nitrogen and, although the cells are technically still alive, all cellular activity ceases. After thawing, up to 50% of sperm will regenerate and can be used for artificial insemination. To ensure that your sperm remain viable after freezing, most centers will run through a freeze-thaw cycle from a semen sample and examine the sperm that survive. Nearly all centers recommend that you bank three or more samples. Sperm can likely be frozen indefinitely, and studies have shown that efficacy rates of artificial insemination are essentially equivalent regardless of whether the sperm came from frozen or fresh semen samples.

As an alternative to banking sperm, extracting sperm directly from

the testicles might be an option. Individual sperm are harvested from testicular tissue, and are prepared for use in a type of artificial insemination known as intracytoplasmic sperm injection. In this procedure, a single microscopic sperm is injected into a single microscopic egg. If an embryo forms, it is implanted into the woman’s uterine wall and allowed to grow. Although technical advances in assisted reproduction have dramatically improved the conception rates, the success rates for the two procedures combined — sperm extraction followed by intracytoplasmic sperm injection — is less than 50%. Note that if there has been radiation damage to the testicles, this approach will not be feasible as no viable sperm will be available for extraction.

Knowing When to Seek Help

As we’ve seen, some form of erectile, urinary, and bowel dysfunction is normal following initial therapy for localized prostate cancer. But it’s important to realize that not all symptoms are normal, and that some require immediate care. If you experience any of the following symptoms, call your doctor or go to an emergency room.

What to look for	Why it is dangerous
Erection lasting for more than four hours or an increasingly cold, bluish penis following vacuum constriction	Lack of fresh circulating oxygenated blood can cause damage to the penile tissue
Inability to urinate or incomplete emptying of the bladder	A backup of urine can cause infections and bladder or kidney damage
Constipation lasting for more than four days	A backup of stool can cause infections and damage to the bowel
Excessive and/or uncontrolled diarrhea	Too much water loss that accompanies diarrhea can lead to dehydration, lightheadedness, fainting, and collapse
Excessive and/or continuous rectal or bladder bleeding	Too much blood loss can lead to lightheadedness, fainting, and collapse or other serious problems; blood clots in the bladder can block the passage of urine

Looking Ahead

Better treatment options for the side effects of primary therapy for localized prostate cancer are currently being researched, but the goal is clearly to reduce the chances of the effects occurring in the first place. As you begin to make some choices about the type of therapy that's right for you, consider which side effects you can live with and which you can't. It's a completely personal decision, one that no one

Anticipating the most likely side effects of therapy will make the effects much easier to deal with afterward.

can — or should — make for you. Anticipating the most likely side effects of whatever therapy you choose and having a sense in advance of how you might want to intervene should it prove necessary will make the

effects that much easier to deal with after therapy. Yes, it's possible that you will experience only minor side effects, and you won't have a need for any of the treatments we discussed above. But any steps that you can take to minimize your side effects will go a long way toward maximizing your quality of life.

CHAPTER 4

Why Nutrition Matters

In the majority of cases, prostate cancer tends to take its time, growing slowly but persistently over the years. This means that, even if you've only recently been diagnosed with prostate cancer, it's likely been growing and developing for many years or even decades. It also means that you might be living with this disease for many more years to come.

Learning how to stay ahead of how the disease progresses and how to address its major symptoms over the long haul is key. But you'll also need to learn how to live with it from day to day, and how to ensure that your diet and lifestyle are in synch with what your body needs to do to fight the disease.

The negative effects of a poor diet and poor exercise habits are all around us. A whopping 65% of adults in the United States are classified as overweight or obese, with a body mass index (BMI) over the accepted norm of 25. Even more disturbing is that 31% of children are classified as overweight or obese, placing them well above the 95th percentile for normal growth for their age. Unfortunately, this increase in weight seems unlikely to be offset by an increase in physical activity, as approximately 40% of adults and teenagers do not exercise regularly.

Where has this over-eating and under-exercising gotten us? The rates for cardiovascular disease, diabetes, cancer, and other chronic diseases are climbing steadily, doing more and more damage to our bodies and claiming the lives of more and more people each year. In men with prostate cancer, obesity can have a negative effect on disease outcomes. Research has shown that PSA test results in obese men can be lower despite the presence of disease, potentially leading to a delay in diagnosis and treatment; recovery from surgery tends to be longer and more difficult; and the risk of dying from prostate cancer can be higher. This means that dietary and lifestyle changes should be an important part of every man's battle with this disease, complementing any drug therapy, surgery, and/or radiation treatment that you might undergo.



In this Chapter, we'll review some of the key findings in nutrition and prostate cancer research, and see how best to incorporate these changes into your life. For an in-depth look at how nutritional elements can affect the development and progression of prostate cancer, see the Prostate Cancer Foundation's *Nutrition and Prostate Cancer* guide.

The Building Blocks: Vitamins and Minerals

The vitamins and minerals found in all foods play an important role in helping to regulate the body's many processes and functions. They can help monitor the balance between cell growth and cell death, and particularly between cancer cell growth and cancer cell death. Con-

tinuing research over the years has shown that the loss of a number of vitamins and minerals can contribute to uncontrolled cancer cell growth — and that, conversely, increased ingestion through foods or supplementation can slow the development and/or progression of prostate cancer.

But supplementation is not always a smart choice. Because

much of our packaged foods — from cereals to orange juice — is fortified with additional vitamins and minerals, true vitamin and mineral deficiency tends to be uncommon in the United States. Therefore, some of the available preparations constitute less a *supplement* and more an *oversupplement*. Why is this a problem? Certain vitamins, such as vitamins A, D, E, and K, are not easily excreted by the body. If taken in extremely high doses, they can build up over time and cause damage to the body's systems. Remember: the best way to increase vitamin and mineral intake is by eating a wide variety of healthy foods.

As you explore the possibility of adding vitamin-rich foods and/or supplements to your diet to help you fight against your prostate cancer, talk with your doctor or qualified nutrition coun-

Dietary and lifestyle changes should be an important part of every man's battle with this disease, complementing any drug therapy, surgery, and/or radiation treatment that you might undergo.

Vitamins and Minerals	Foods
Vitamin A	Apricots, lettuce, spinach, chicken livers
Vitamin B6	Fortified cereals, chickpeas, nuts
Vitamin C	Citrus fruits and juices, red peppers, grape juice
Vitamin D	Sunlight, fortified milk
Vitamin E	Fortified cereals, tomato-based products, nuts, spinach
Beta-carotene	Carrots, pumpkin, sweet potatoes, spinach
Calcium	Dairy products, collard greens, sardines with bones
Lycopene	Tomato-based products, watermelon, pink grapefruits, guava, papaya
Selenium	Nuts, fish, whole-grain wheat flour, garlic
Zinc	Raw or cooked oysters, beef, crab

Source: U.S. Department of Agriculture, Agricultural Research Service. 2004. USDA Nutrient Database for Standard Reference, Release 17. Available at http://www.nal.usda.gov/fnic/foodcomp/Data/SR17/wtrank/wt_rank.html.

selor about establishing a safe balance between healthful vitamin intake and oversupplementation. Remember, vitamin and mineral supplements are meant to be just that, supplements. They should not be used in place of smart food choices but should be used judiciously in the appropriate setting.

Finally, keep in mind that many supplements can interact with medications you might be taking. They can change the way that the medications act, making them stronger or weaker than desired, and can cause an increase in unwanted side effects. Be sure to talk with your doctors and nurses before you consider taking any supplements. This way, you can make sure that you get the maximum benefit from your medications as well as from the additional vitamins and minerals.

Vitamin and mineral supplements can interact with medications you might be taking; be sure to talk with your doctors and nurses before you consider taking any supplements.

	Recommended Intake*	Upper Intake† Level
Vitamin A	3,000 IU/day	10,000 IU/day
Vitamin B6	1.7 mg/day	100 mg/day
Vitamin C	90 mg/day	1,800 mg/day
Vitamin D	400 IU/day	2,000 IU/day
Vitamin E	22.5 IU/day	1,500 IU/day
Calcium	1,200 mg/day	2,500 mg/day
Selenium	55 mcg/day	400 mcg/day
Zinc	11 mg/day	40 mg/day

Values are for healthy males aged 19-70 years.

*Recommended dietary allowances or adequate intakes to be used as goals for individual intake. †The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects; represents total intake from food, water, and supplements.

Source: Institute of Medicine of the National Academies. Dietary reference intakes.

Available at <http://www.iom.edu/Object/File/Master/21/372/0.pdf>.

Changing Your Dietary Habits One Tomato at a Time

A recent study evaluating four popular weight-loss plans showed that the majority of the dieters dropped out within just a few months. But those who were enrolled in programs that could be more easily adaptable to the ups and downs of everyday life stuck to their diets for a longer time. The lesson here is clear: integrate smarter choices gradually, making simple, small changes to your existing diet on a regular basis. After just a few short months, you'll be set on a road toward a healthier lifestyle.

So what changes should you be making in your fight against prostate cancer? Much of the nutrition research completed to date has focused on how to lower your risk for developing the disease. But as we'll see, research has also shown that prostate healthy = heart healthy = life healthy. So even if we have yet to prove that a particular dietary change can affect how your disease progresses, sticking to the broad guidelines that we'll outline here can help you live a healthier life all around, which, in turn, will keep your body strong to help fight off your disease.

Fruits and Vegetables

A number of studies have looked at the benefit of fruits and vegetables as part of an overall healthy diet. In addition to being chock full

of vitamins and minerals, they're a good source of fiber, which has been shown to reduce the risk of developing heart disease, and are low in calories and fat, which can help ward off the risk of developing diabetes.

Let's look at the tomato, a fruit that has been widely touted as being "prostate healthy." A medium red tomato has fiber, protein, vitamin A, vitamin C, potassium, beta-carotene, and lycopene — a nutrient that has been widely studied as a possible contributor in reducing the risk of developing both prostate cancer and heart disease.

But there's another reason to increase your fruits and vegetables. The *Dietary Guidelines for America*, published jointly by the US Department of Health and Human Services and the US

Department of Agriculture, recommends that you eat 5 to 9 servings a day of fruits and vegetables. A realistic goal? Maybe, maybe not. But most people set an upper limit on the quantity of food that they consume on an average day, so even if they can't hit that number each day, they are most likely reaching the minimum recommended number. Remember: for every extra bite of vegetable that's eaten, there's a bite of unhealthy, fat- and calorie-laden food that's going uneaten. In this case, more is definitely better.

Red Meat vs Fish

Today's dietary world is divided into good foods and bad foods. In this accounting, red meat is a bad food. It has a prominent place in the "Western-style" diet that underlies the poor nutritional habits of Americans today. Red meat has acquired the reputation of being filled with fats, carcinogens, growth hormones, and antibiotics, but red meat is also an excellent source of protein, iron, zinc, vitamin B6, and vitamin B12. So simply cutting it out of the diet without replacing it with something else that is just as nutritious is not a smart choice.

A number of years ago, the omega-3 fatty acids found primarily in fatty fish, fish oils, and certain vegetable oils, including walnut and

For every extra bite of vegetable that's eaten, there's a bite of unhealthy, fat- and calorie-laden food that's going uneaten. In this case, more is definitely better.

canola oils, were studied for their beneficial effects. In fact, studies have shown that, in some men, the addition of a few servings of fatty fish high in omega-3 fatty acids each week might reduce the risk of having a heart attack and might reduce the risk of developing advanced prostate cancer.

How these benefits will affect you individually is unknown, but replacing red meat with fish a few times a week would seem to be good way to offset some of the “bad” aspects of red meat while picking up some of the “good” aspects of fish.

Exercise

The *Dietary Guidelines for America* recommends exercising at least 30 minutes a day at least 3 days each week. At this rate, studies have shown small reductions in the risk of developing advanced prostate cancer as well as improvements in body weight, blood pressure, serum cholesterol, and glucose tolerance, each of which is a separate risk factor for heart disease.

But there are other reasons that exercise is important. Regular stretching exercises will help keep muscles limber and flexible, while

resistance exercises and weight training will help maintain muscle strength and endurance, help to decrease your risk for developing osteoporosis, and increase bone strength and structure. Walking, jogging, playing tennis or golf, and even

Walking, jogging, playing tennis or golf, and even gardening can be effective forms of exercise — the key is to stay on the go and stay off the couch.

gardening can be effective forms of exercise — the key is to stay on the go and stay off the couch.

Nutritional Approaches and Therapeutic Strategies Go Hand in Hand

Dietary and lifestyle changes can play an important role in slowing the growth of prostate cancer, but they should *complement*, not replace, any drug therapy, surgery, and/or radiation treatments that might be recommended by your physician. Be sure to talk with your doctor before initiating any diet and lifestyle changes, particularly if

you have any medical conditions that affect your daily life, such as diabetes or heart disease.

As you plan out any changes you might be making, follow the recommendations of your doctors, nurses, and/or qualified nutritional consultant to ensure that you're receiving the maximum benefit. Your goal of staying as healthy and strong as possible can only be achieved if you eat a well-balanced, nutritious diet.

Remember, it's the *quality* of the effort that counts, not the *quantity*. A diagnosis of prostate cancer is the beginning of your journey, not the end. Every small step toward a healthier lifestyle is important and will ultimately contribute to your efforts in battling this disease.

CHAPTER 5

“Secondary” Local Treatment

When prostate cancer is caught in its earliest stages, initial therapy can lead to high chances for cure, with most men living cancer-free for five years. But prostate cancer can be slow to grow following initial therapy, and it has been estimated that about 30% of men will relapse after the five-year mark and begin to show signs of disease recurrence.

A rising PSA is typically the first sign seen, coming well before any clinical signs or symptoms. How high is too high for the PSA to rise to be of concern? At what point should additional treatment be considered? Which treatments should be attempted?

In this Chapter, we’ll look at what happens when PSA first starts to rise after surgery or radiation therapy, and why a secondary local treatment might be right for you.

PSA as a Marker for Disease Progression

As we discussed earlier, when it comes to assessing disease progression, PSA is widely accepted as an invaluable tool.

PSA is produced by all prostate cells, not just prostate cancer cells. At this point in your journey, your cancer cells have either been removed or effectively killed after being bombarded with radiation. But some cells might have been able to spread outside the treatment areas before they could be removed or killed. These cells at some point begin to multiply and produce enough PSA that it can again become detectable by our lab tests.

Therefore, PSA is not really a marker for disease progression, but a marker for prostate cell activity. Because the two correlate well after initial treatment for local therapy, tracking the rise of PSA in this setting is an important way of understanding how your prostate cancer is progressing.

However in order to determine whether your PSA is rising, you need to first determine where it is rising *from*.



After prostatectomy, the PSA drops to “undetectable levels,” typically given as < 0.05 or < 0.1 , depending on the lab. This is effectively 0, but by definition we can never be certain that there isn’t something there that we’re just not picking up. By contrast, because normal healthy prostate tissue isn’t always killed by radiation therapy, the PSA level doesn’t drop to 0 with this treatment. Rather, a different low point is seen in each case, and that low point, or *nadir*, becomes the benchmark by which to measure a rise in PSA.

Because the starting point is different whether you had surgery or radiation therapy, there are two different definitions for disease recurrence as measured by PSA following initial therapy.

In the post-prostatectomy setting, the most widely accepted definition of a recurrence is a PSA > 0.3 ng/mL that is seen to be rising on at least two separate occasions at least two weeks apart and measured by the same lab. In the post-radiation therapy setting, the most widely accepted definition is a PSA that is seen to be rising from nadir in at least three consecutive tests conducted at least two weeks apart and measured by the same lab. It’s important to always use the same lab for all of your PSA tests because PSA values can fluctuate somewhat from lab to lab.

The reason that we need to look for confirmation from multiple tests following radiation is that the PSA can “bounce” or jump up for a short period after radiation therapy, and will then come back down to its normal level. If we relied only on the one elevated PSA, it’s possible that we will have tested during a bounce phase, and the results will therefore be misleading. This PSA bounce typically occurs between 12 months and 2 years following the end of initial therapy.

If your PSA is rising but doesn’t quite reach these definitions, your doctor might be tempted to start initiating further therapy anyway. Remember that PSA is only one of many factors that help to determine your prognosis after treatment. The original clinical stage of disease, your pre-diagnostic PSA, and your overall health and life expectancy are also key factors in assessing the aggressiveness of your disease, so be prepared to discuss treatment options even if you don’t fit the classical categories for PSA rise after initial therapy.

On the other hand, if your PSA is rising and you do fit the categories defined above, that doesn’t necessarily mean that your situation is dire. What researchers have been finding over the past few

years is that universal PSA cut-offs might not be sufficient for truly understanding how prostate cancer grows.

PSA Velocity

Suppose one man underwent intensity-modulated radiation therapy (IMRT), and his PSA nadir was 0.15 ng/mL. Over the course of nine months, it slowly creeps up until it hits 0.45. But his brother, who also underwent IMRT, nadired at 0.32 ng/mL. If after the same progres-

sion over the course of nine months his PSA also rose to 0.45, are they now in the same place? Or is there some significance to the fact that one man's PSA rose much more rapidly than his brother's?

The rate at which your PSA rises after prostatectomy or radiation therapy can be a very

Although a rising PSA can indicate that prostate cancer is progressing, it is only one of many factors that help to determine your prognosis after treatment.

significant factor in determining how aggressive your cancer is, and can therefore be useful in determining how aggressively it might need to be treated.

When looking at PSA velocity in a few hundred men who had undergone either prostatectomy or radiation therapy, researchers found that men whose PSA doubled in under three months had the most aggressive tumors and were more likely to die from their disease, whereas those whose PSA doubled in more than ten months had the least aggressive tumors and were less likely to die from their disease.

If we go back to our two hypothetical cases, although both have a PSA of 0.45 ng/mL, the first one, whose PSA rise represents a doubling within nine months after treatment, would likely be considered for an aggressive therapeutic regimen. And the second case with the smaller rise in PSA? He might be watched closely to see how rapidly his PSA rises, and to determine when it might be time to intervene.

However, PSA doubling time or velocity does not always remain the same over time. So even if you have a very slowly rising PSA now, continued monitoring with your doctor is important. Also, if you've consistently kept to a very low PSA rate after treatment, *any* rise will

likely be seen as a signal that the tumor might be starting to grow again.

Measuring and using PSA velocity is an art, not a science. There's no magic number of times that your PSA has to be tested in order to determine the rate of rise, although most researchers would agree that more frequent tests over longer periods of time will likely give a better sense of how your tumor is growing.

Ultimately, PSA is only one of many factors that can influence the decision to pursue additional treatments. You and your doctors will need to weigh all of the different factors before deciding on the course that's right for you.

Radiation Therapy Following Prostatectomy

If your PSA starts to rise after you've undergone prostatectomy, so-called "salvage" radiation therapy might be a good option to explore. With this approach, external beam radiation is delivered to the area immediately surrounding where the prostate was, in the hopes of eradicating any remaining prostate cells that have been left behind. (Brachytherapy is not an option because there is no prostate tissue in which to embed the radioactive seeds.)

But the procedure is not for everyone. If there are obvious sites of disease outside of the immediate local area, if any tumor cells have been found in your lymph nodes, or if your Gleason score was 8-10, post-surgery radiation therapy is probably not right for you. Also, in men who are considered good candidates for this therapy, it can be very effective, but five-year disease-free rates tend to be considerably higher in men whose pre-therapy PSA levels are lower than 1.0 ng/mL compared with those whose pre-therapy PSA levels are greater than 1.0 ng/mL. Therefore, if you and your doctors are considering post-surgery radiation, ideally you should start before your PSA goes above 1.0 ng/mL.

Side effects from the radiation therapy can be moderately severe,

If your PSA starts to rise after prostatectomy, you might be a candidate for "salvage" external beam radiation therapy delivered to the area surrounding where the prostate was.

and are additive to those previously received with surgery. Be sure to discuss with your doctors what you can reasonably expect before deciding on a course of therapy. In some cases, hormone therapy might be added for a short period before or during the radiation treatment, which can also add to the side effects that you might experience.

Because the anatomy looks different and the tumor is often not visible on imaging or felt on DRE, the radiation oncologist has to carefully balance between delivering sufficient radiation to destroy the prostate cells while not damaging the healthy tissue. Once again, practitioner skill can make an important difference in outcomes.

In some cases, particularly if the tumor was considered high-grade and therefore at greater risk of spreading to the surrounding areas, your doctor might decide to initiate radiation therapy right after you've healed from your surgery. This approach, known as *adjuvant* therapy, typically starts about six weeks after surgery, and is unrelated to "salvage" radiation therapy that is administered if the PSA begins to rise.

Prostatectomy Following Radiation Therapy

Traditionally, one of the key factors when deciding between prostatectomy and radiation for initial treatment was the issue of secondary local therapy. Because radiation therapy resulted in great damage to the genital area, curative surgical resection of the remaining prostate and/or tumor tissue was difficult. Many men therefore opted for surgery simply because it gave them the opportunity to be treated afterward with radiation therapy, should their cancer return.

With the advent of 3-D conformal radiotherapy, IMRT, and brachytherapy, local tissue damage is often kept at a minimum, and surgeons at some of the larger cancer centers have been seeing improved results with "salvage" prostatectomy. Much of the data suggest that men who had tumors that were considered potentially curable before radiation might do well with post-radiation surgery. But if the tumor had characteristics that suggest a higher likelihood of early disease recurrence, such as a higher Gleason score or spread to the lymph nodes or seminal vesicles, the surgery will probably offer little or no benefit.

Nevertheless, even under the best of circumstances, post-radiation surgery is a very difficult operation to perform and can result in significant urinary and erectile dysfunction, so few surgeons across the country perform it regularly. If you talk with your doctors about this treatment approach, be sure to carefully weigh all of the different factors that can play a role in determining whether this approach is right for you.

Brachytherapy Following External Beam Radiation Therapy

The use of radioactive seed implantation after external beam radiation therapy has five-year disease-free rates around 50%. Because this approach delivers radiation to very localized areas, it is not an optimal treatment for men with tumors that have spread beyond the prostate. Studies to date have indicated that men with low pre-therapy PSA levels and low Gleason scores will likely do well, whereas those with more distant disease and short PSA doubling times fare worse.

As with brachytherapy used as a primary therapy, side effects tend to be less frequent and less severe compared with other therapies. However, some studies have found urinary incontinence rates of up to 25% in men undergoing “salvage” brachytherapy, so careful consideration of existing urinary function and expected loss of function should be discussed fully with your doctors before any decision is made.

Cryotherapy Following Radiation Therapy

As we noted in Chapter 2, cryotherapy is an option worth exploring, particularly for men who have other health problems that might impair their recovery from a surgical procedure. In the same vein, cryotherapy has been used as a secondary local therapy in men who

Post-radiation surgery remains technically challenging, but surgeons at some of the larger cancer centers have shown better results as radiation therapy techniques improve.

underwent radiation therapy, and has shown five-year disease-free rates around 40%. However, because the procedure does not completely destroy all remaining prostate cells, the PSA generally does not drop to 0, so it is often difficult to determine complete success. Men with lower pre-cryotherapy PSA levels and lower Gleason scores tend to fare better, while those who received hormone therapy in addition to radiation therapy tend to fare worse.

Side effects of cryotherapy tend to be milder compared with standard prostatectomy, and the same holds true when used after radiation therapy. Nevertheless, rates for erectile dysfunction following this procedure remain high, as do rates for pelvic or rectal pain. Because the severity of side effects tends to correlate with the amount of tissue that is frozen during therapy, better techniques that are currently being studied might improve outcomes over time.

Summing It All Up

When looking at the different options for secondary local therapy, two things become very clear. First, practitioner skill and expertise remain crucial to the success of these treatment options. Surgeons must navigate through radiation-damaged tissue, and radiation oncologists

must orient the dose planning around the anatomical changes caused by surgery. Greater experience at performing these types of procedures will help to minimize side effects while maximizing efficacy.

Second, and most importantly, the best outcomes are

seen in those men whose PSA levels are low and whose disease has not spread too far. Primary therapy can be curative, but does not always result in 100% long-term disease-free survival rates. Regular monitoring of PSA levels after primary therapy is key, as is prompt initiation of treatment upon disease recurrence. The earlier the treatment is begun, the better the likelihood of improved results.

Regular monitoring of PSA levels after initial therapy is key, as is prompt initiation of treatment upon disease recurrence.

CHAPTER 6

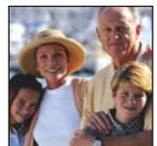
Using Hormone Therapy

Prostate cancer cells are just like all other living organisms — they need fuel to grow and survive. Testosterone, a hormone that is responsible for what we consider the typical male characteristics such as body hair growth and increased muscle mass, is also the main fuel for prostate cancer cell growth and is therefore a common target for therapeutic intervention in men with prostate cancer.

Treatment regimens that fall into this category are commonly known as “hormone therapy” or “hormonal therapy,” but should really be called “anti-hormone therapy.” The goal is to stop testosterone from being released or to prevent the hormone from acting on the prostate cells. (An alternative name for this treatment, androgen deprivation therapy, or ADT, probably offers the most accurate description.)

In past decades, men with localized prostate cancer were treated with surgery or radiation therapy, and only came back to their doctors for additional treatment, specifically hormone therapy, if they experienced pain or other symptoms indicating that their cancer had recurred and had metastasized, or spread to other areas of the body. In fact, the shift from early-stage to advanced prostate cancer is often characterized by the need for systemic therapies, or those that work throughout the whole body instead of just at the local tumor site, in order to keep the disease under control. The use of hormone therapy in men with metastatic prostate cancer has been the standard of care for over 60 years. However, more and more researchers are finding that the lines between local and systemic treatments are blurred, and that some men with early disease might benefit from hormone therapy either before, during, or after local treatment.

In this Chapter, we’ll review the ways in which different hormone therapy options can be used in men with prostate cancer. As we’ll see, because the process by which testosterone affects cell growth has multiple steps, researchers have identified a number of different drugs and surgical options that can be used effectively. But remember that no one



A BRIEF REVIEW OF MEDICAL-SPEAK

People often think that doctors use complicated, important-sounding words so they can impress non-doctors. Truth is, it's sometimes important to use the complicated words because they more accurately describe exactly what's going on.

The term *advanced* prostate cancer is typically used to describe prostate cancer that has spread beyond the prostate and that requires systemic therapies, or those that work throughout the whole body instead of just at the local tumor site. But if you read through the medical literature, you'll more often come across phrases like *hormone-sensitive*, *hormone-refractory*, or *metastatic* disease; some publications will use the terms *androgen-dependent* and *androgen-independent* instead of hormone-sensitive and hormone-resistant. In each of these cases, the prostate cancer is considered "advanced," but the more descriptive terms allow doctors to better understand what's happening with the tumor and to describe its potential for response to hormone therapy.

When the tumor has progressed beyond the local stage and hormone therapy is considered, the tumor is nearly always described in relation to how it does — or does not — respond to hormones. Tumors that are *hormone sensitive* are those that slow or stop growing when hormone therapy is introduced; tumors that are characterized as *hormone-refractory* or *androgen-independent* have stopped responding to, or are growing despite the use of active hormone treatment strategies, at which point other options, such as chemotherapy, are often considered.

approach is right or wrong. Be sure to discuss the different options with your doctor so you can find the approach that's right for you.

Why Hormone Therapies Work

As we mentioned earlier, the goal of all hormone therapies is to somehow interfere with the way that testosterone acts on the prostate cancer cells and allows them to grow. Although this is true in the broad sense of prostate cancer, in reality, not all cells are sensitive to increases or decreases in testosterone levels, making hormone ther-

Metastatic disease refers to the stage in which metastases (singular is *metastasis*) have been detected. A metastasis is a tumor that is growing in an area outside of where it originated. For example, if a prostate tumor starts growing in the bone, it's not considered bone cancer, but a prostate cancer bone metastasis. Depending on where they are, metastases can often be detected on x-rays, CT scans, MRIs, or specialized bone scans. Once they're detectable, treatment options always include systemic drugs, because the treatments have the ability to travel around the body and either slow the growth of or kill whatever cancer cells they can find. But it can often take a while to reach this stage because although we know that prostate cancer cells have reached this new area by traveling through the bloodstream and most likely have traveled to other areas as well, we can't see them when the clusters of cells are very small.

Hormone sensitive tumors will slow or stop growing when hormone therapy is introduced; hormone-refractory or androgen-independent tumors don't respond to active hormone treatment strategies.

Although these classifications are convenient, they're rarely perfect, and all doctors know that. Prostate cancers are fickle, and don't always run the exact same course in all men. But the classifications give doctors a general sense of where you are in your journey through this disease, and therefore a better appreciation for which treatment options might be right for you.

apy a somewhat imperfect weapon in the fight against prostate cancer. It is therefore important to understand that hormone therapy is a treatment for prostate cancer but does not cure the disease.

Think about the last time you had an infection that required antibiotics. The doctor gave you a prescription for a few days' worth of antibiotics, and you took all of the pills as prescribed. By the end of the course of therapy, the pills had killed off the infection and you were all healed, right? Well, not exactly.

Each type of antibiotic is very effective against a particular group of bacteria. But it's not uncommon to have a few different groups of

bacteria in your system at any one given time. The antibiotic that you took killed off the majority of the bacteria, and likely left a small amount that it was unable to affect. And that's ok, because your body at that point was strong enough to fight off the remaining bits of infection on its own, without any help from the pills.

When it comes to prostate cancer, the process is the same, but with two very important differences. First, although the body is usually strong enough to fight off a low-level infection, it's rarely strong enough to fight off cancer on its own. Because the majority of the cells in prostate cancer tumors respond to the removal of testosterone, hormone therapies can

The majority of prostate cancer cells respond to the removal of testosterone; cells that grow independent of testosterone remain unaffected and grow unchecked.

keep the cancer under control. But the cells that grow *independent* of testosterone remain unaffected and grow unchecked. Which means that after some period of time — maybe a few months, more likely a few years, maybe even a

decade or more — those hormone-independent prostate cancer cells will become strong enough that hormone therapies will have less and less of an effect on the growth of the tumor.

Second, antibiotics actually kill the bacteria; hormone therapies can kill cancer cells, or in many instances, merely slow down the growth of prostate cancer cells. Which is why the therapies are continued even *after* the hormone-independent cells have grown enough to start causing trouble. It's true that the therapies can't affect the growth of the independent cells, but the hormone-sensitive ones are still there, and still need to be kept under control.

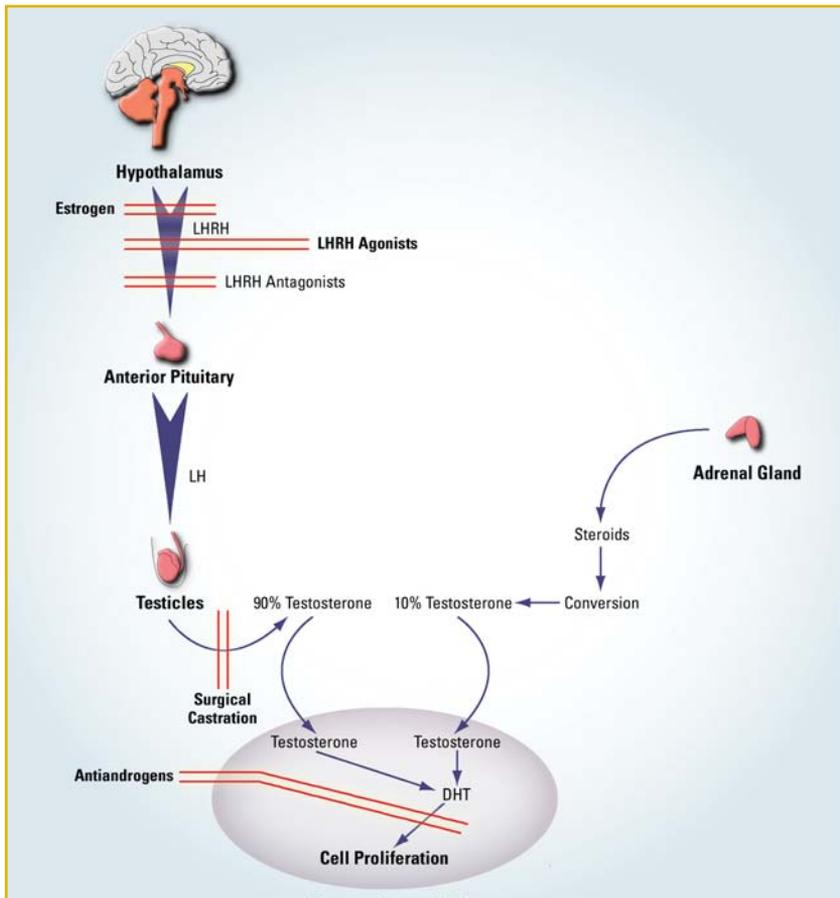
How do we know when the balance has begun to shift in favor of the hormone-independent cells? Your PSA levels will let us know. Just as a rising PSA following prostatectomy or radiation therapy is an early warning sign that the cancer has started to grow again, a rising PSA *despite* hormone therapy is an early warning sign that the tumor is becoming less and less sensitive to the changes in testosterone. A rising PSA doesn't mean that the hormone therapy isn't working, it simply means that it's not working enough, and that it might be time to start investigating other options.

Hormone therapy is not a perfect strategy in the fight against prostate cancer, and, on average, is effective for only a few years. But it remains an important step in the process of managing advancing disease, and will likely be a part of every man's therapeutic regimen at some point during his fight against recurrent or advanced prostate cancer.

How Hormone Therapies Work

In order to better understand how the different anti-testosterone treatments work, it's helpful to review the basic mechanisms behind testosterone production and release.

The delicate interplay among hormones and prostate cancer cell growth



Adapted with permission from Lippincott Williams & Wilkins. Hellerstedt BA, Pienta KJ. The current state of hormonal therapy for prostate cancer. CA Cancer J Clin. 2002;52:154-179.

Blocking Testosterone Release

The hypothalamus is a small structure in the brain that helps to regulate many of the normal metabolic functions such as body temperature and water balance. Part of the way that it does this is by releasing chemicals that trigger other parts of the body to release hormones. The first step in testosterone release occurs when the hypothalamus releases luteinizing-hormone releasing hormone (LHRH), which causes the pituitary gland at the base of the brain to release luteinizing hormone (LH). LH, in turn, stimulates the testicles, or testes, to secrete testosterone. (Note that LHRH is sometimes called GnRH, or gonadotropin-releasing hormone.)

Because LHRH release is the first step in this process, one common therapeutic strategy to block the secretion of testosterone is the use of LHRH agonists or analogues. These drugs mimic the action of LHRH, and effectively force the system to shut down because of LHRH overload. Upon shut-down, the testicles receive no signal to produce or secrete testosterone, so the factory production lines are halted. Drugs in this class include leuprolide (Eligard, Lupron, and Viadur), goserelin (Zoladex), and triptorelin (Trelstar).

The LHRH antagonist abarelix (Plenaxis) directly prevents the release of LHRH by the hypothalamus. As of this writing, this drug has been discontinued by the manufacturer and is now only available to men who had already been receiving it from their doctors. No other LHRH antagonists are as yet available.

As an alternative to drug therapy, the surgical removal of the testicles, known as orchiectomy or surgical castration, will shut down the testosterone factory in the testicles permanently. This approach has been used successfully since the 1940s, but because it's a permanent and irreversible surgical solution, most men opt for drug therapy instead.

Some advantages to orchiectomy include its low cost and simplicity compared to multiple years' worth of LHRH agonists: the procedure is performed on an outpatient basis in your urologist's office and regular LHRH injections are not needed.

A final option in this setting is the use of estrogens, hormones that inhibit LHRH release from the hypothalamus. Like orchiectomy, the estrogens were used early in prostate cancer research studies, and have proven effective in many men. But it has also been linked to an increase in cardiovascular side effects and, because it is one of the

main hormones that affect female characteristics, signs of demasculinization such as increased breast size and tenderness, are commonly seen. Typically, doctors will save this option for men whose PSA levels are rising after they start to lose their sensitivity to hormone therapy.

Blocking Testosterone Action

Once testosterone is released from the testicles, it is converted into dihydrotestosterone (DHT). DHT, in turn, crosses into the nucleus or central part of the cells and promotes the synthesis of PSA and the growth of prostate cancer cells.

Antiandrogens such as bicalutamide (Casodex), flutamide (Eulexin), and nilutamide (Nilandron), block DHT action in the cell and can therefore play an important role in preventing testosterone action. Although these agents can be used on their own, as we'll discuss in more detail below, they're more commonly used in combination with the LHRH agonists. Also, as we'll discuss below, adding or subtracting these agents is a useful strategy in men whose PSA levels are rising as they start to lose their sensitivity to hormone therapy.

Using Hormone Therapy

One of the downsides of having so many different types of drugs for use in a particular disease or disorder is figuring out what to use when. With hormone therapy, it's even more complicated, because each class of drugs works in a very different way, and, unfortunately, our understanding of the mechanisms behind these drugs remains poor.

When deciding on exactly which hormone therapy to use, discuss with your doctor the potential benefits and side effects of each drug, and, most importantly, which options are available to you in case your first attempt doesn't completely work, work for long enough, or stops working. It's no reflection on you or on your disease if the drug that you choose doesn't keep your PSA down as you

People respond to the different hormone therapies in different ways; the challenge is finding the drug, or combination of drugs, that's right for you.

had hoped. People respond to the drugs in different ways; the challenge is finding the drug, or combination of drugs, that's right for you.

Orchiectomy

When prostate cancer treatments were first being developed in the 1940s, the goal was clear — eliminate the testosterone and the tumor stops growing. The obvious solution therefore was to surgically remove the testicles that produce the testosterone. Over the years, however, as researchers began to understand better the dynamics behind testosterone production, they realized that surgery might not always be necessary, and that drug therapy can be equally effective. Nevertheless, the surgery, known as orchiectomy, is still done. If your doctor recommends surgery, don't automatically assume that he or she is out of the Dark Ages. After discussing the pros and cons, you might find that surgery is right for you.

In men who choose this path, the surgeon will remove both testicles from within the scrotum. To preserve a more natural look, prosthetic silicone-based testicles can be placed within the scrotum. Alternatively, a subcapsular procedure can be done, whereby only the tissue inside the testicle's capsule, or outer casing, is removed; because the capsule is left inside the sac, the testicle retains its shape. Regardless of how the procedure is done, recovery from surgery tends to be rather quick and no further hormone therapy is needed, making orchiectomy a very attractive choice for someone who prefers a low-cost, one-time procedure rather than undergo regular injections of LHRH agonists. Note that because sperm are generated in the testicles, men who undergo bilateral orchiectomy are rendered irreversibly infertile. (A discussion of ways to preserve sperm before treatment is in Chapter 3.)

LHRH Agonists

By far, the most commonly used hormone therapy drug class is the LHRH agonists or LHRH analogues. Clinical trials have shown that their use provides the same benefit as does surgical removal of the testes, but for obvious reasons is typically preferred by men over surgery. LHRH agonists are given in the form of regular shots: once a month, once every three months, once every four months, or once per year. These long-acting drugs are injected under the skin and

most of them form into a time-release “pellet” that releases the drug slowly over time. While some men might prefer the longest-acting of these time-release drugs to avoid regular drug injections, many physicians prefer the flexibility of using shorter-duration dosing so that treatment can be adjusted or changed if and when the need arises. Keep in mind that the injections must be administered regularly for life, so if you have a fear of needles or tend to find them painful, “medical castration” with LHRH agonists might not be the best choice for you.

Typical dosing schedules for LHRH agonists used in the United States

Agents	Dosing Schedule
Leuprolide <i>Eligard</i>	7.5 mg once a month
<i>Lupron Depot</i>	22.5 mg once every 3 months 30 mg once every 4 months 7.5 mg once a month
<i>Lupron Injection</i>	22.5 mg once every 3 months
<i>Viadur Implant</i>	30 mg once every 4 months 65 mg once every 12 months
Goserelin <i>Zoladex</i>	3.6 mg once every 28 days 10.8 mg once every 3 months
Triptorelin <i>Trelstar Depot</i>	3.75 mg once a month
<i>Trelstar LA</i>	11.25 mg once every 3 months

Antiandrogens

The sexual side effects of the antiandrogens when given alone are typically far fewer compared with the LHRH agonists. They therefore can be a good option for men who are concerned about the effects of testosterone loss, but might not be as effective as orchiectomy or LHRH agonists and are not the optimal choice for men with documented metastatic prostate cancer.

As described in more detail above, LHRH agonists cause what is known as a “flare” reaction because of an initial transient rise in testosterone. This can result in a variety of symptoms ranging from bone pain to urinary frequency or difficulty. To counteract this

Typical dosing schedules for antiandrogens when used in combination with LHRH agonists

Agents	Dosing Schedule
Bicalutamide <i>Casodex</i>	50 mg once daily
Flutamide <i>Eulexin</i>	250 mg once every 8 hours
Nilutamide <i>Nilandron</i>	300 mg once daily for 30 days then 150 mg once daily

effect, an antiandrogen is often added to the LHRH agonist for at least the first 4 weeks of therapy when the flare typically occurs. In this setting, antiandrogens can be helpful in preventing the flare reaction.

Managing the Effects of Testosterone Loss

Testosterone is the primary male hormone, playing an important role in establishing and maintaining the typical male characteristics, such as body hair growth, muscle mass, sexual desire, and erectile function, but also controlling many other physiologic effects that we don't typically think of as hormone related. The list of potential effects of testosterone loss is long: hot flashes, decreased sexual desire, erectile dysfunction, fatigue, osteoporosis, weight gain, decreased muscle mass, anemia, and

Before you begin hormone therapy, discuss the effects of testosterone loss with your doctor so you can alter your lifestyle to accommodate or head off the changes.

memory loss. Most men who are on hormone therapy experience at least some of these effects, but the degree to which you will be affected by any one drug regimen is impossible to predict.

Before you begin hormone therapy, be sure to discuss the effects of testosterone loss with your doctor, so you can alter your lifestyle to accommodate or head off the changes.

Intermittent Therapy

Although the LHRH agonists (with or without the addition of an antiandrogen) are very effective at keeping the cancer at bay for periods of time, the resultant loss of testosterone can have significant side effects in many men. Over the years, researchers have explored different ways to minimize these side effects. The most commonly explored strategy is known as *intermittent therapy*.

This strategy takes advantage of the fact that it takes a while for testosterone to begin circulating again after LHRH agonists are removed. The LHRH agonist is used for six to twelve months, during which time a low PSA level is maintained. The drug is stopped until the PSA rises to a predetermined level, at which point the drug is restarted. The “drug holidays” in between cycles allow men to return to nearly normal levels of testosterone. Sexual function and other important quality of life measures might return before the next cycle begins again.

From a treatment perspective, there might be a benefit as well to intermittent therapy. As we discussed earlier, hormone therapy is a temporary solution, as the hormone-independent cells eventually become strong enough that hormone therapies will have less and less of an effect on the growth of the tumor. Laboratory studies have shown that the intermittent approach exploits this feature, and allows the cells that are sensitive to hormone therapies to grow during each “off” cycle, potentially extending the hormonal sensitivity of the tumors.

At this time, the true benefits of this approach remain unclear, and large clinical trials are currently underway to evaluate its use in men with advanced prostate cancer. If the approach proves to be as effective as continuous therapy in suppressing tumor growth, intermittent therapy will likely become popular because of potential for an improved side effect profile.

Early vs Deferred Hormone Therapy

As we’ve noted earlier, hormone therapy is a staple in the management of metastatic prostate cancer. But researchers have been looking into whether there might be an added benefit if hormone therapy is initiated earlier, once the PSA level in the blood starts to rise following prostatectomy or radiation therapy.

The clearest downside to early initiation — outside of the side effects — is the temporary nature of hormone therapy. On average, hormone therapy keeps PSA levels and tumor growth at bay for about two to three years, after which the hormone-independent cancer cells grow enough to start causing trouble and other treatment approaches must be tried. Given this short time span, some have argued that starting hormone therapy early limits the treatment options of men with advancing prostate cancers.

In addition, because it can take some time for prostate cancer metastases to show up on CT or MRI scans, it remains difficult to know whether the additional therapy actually affects the growth of the tumor cells. This, therefore, raises the question of whether it is prudent to subject someone to the effects of the additional therapy if there's no way to prove whether it's effective.

Deferring hormone therapy until metastatic disease can be detected might be an appropriate option for some men. In such cases, the goal would be to reserve an effective, albeit temporary, treatment option until it's clearly needed.

On the other hand, data from other cancer types, such as breast cancer, have shown that using more therapy early on might be able to improve outcomes from primary therapy in some people.

Keeping these opposing views in mind, prostate cancer researchers have tried to identify strategies that minimize the amount of hormone therapy administered in the earliest stages while maximizing its effect on cancer growth. To date, most research has been done with the use of neoadjuvant hormone therapy before primary radiation therapy, and studies have found that its use in this setting might be beneficial for some men.

Neoadjuvant Hormone Therapy

In women with breast cancer, the purpose of neoadjuvant therapy (*neo*, meaning before; *adjuvant*, meaning as an adjunct to) is to shrink the tumor so that a breast conserving surgery, or lumpectomy, can be performed. Typically, a course of just a few months of therapy is enough to accomplish this goal. This treatment might also be sufficient to eliminate microscopic disease that may be present elsewhere in the body but too small to be detected by any scan.

Results from clinical trials that have looked at the benefits of

neoadjuvant hormone therapy in men undergoing primary radiation therapy have shown improved outcomes with its use, but there doesn't seem to be much benefit for men undergoing prostatectomy.

Why there would be a difference between the two remains unclear but two main theories have been proposed. First, the hormone therapy weakens the cancer cells in the prostate, making them more sensitive to radiation. Second, the hormone therapy might eradicate hidden metastatic disease elsewhere in the body in men with more aggressive cancers, particularly those with Gleason scores above 7.

Because of the boost that neoadjuvant hormone therapy gives to radiation therapy, the approach is now used in many institutions for men with high-grade or bulky cancers.

The boost that neoadjuvant hormone therapy gives to the success of radiation therapy has resulted in the approach becoming the standard of care in many institutions for men with high-grade cancers and/or those with larger, bulkier tumors.

In this setting, LHRH agonists, antiandrogens, or a combination of the two are given for three to six months, after which the radiation therapy begins.

When reviewing the different treatment options, be sure to discuss with your doctors whether a short course of neoadjuvant hormone therapy before radiation therapy might be right for you, and whether continuing the hormones afterwards might be beneficial.

Options for “Secondary” Hormone Therapy

As we noted earlier, hormone therapy typically is effective for only a few years. After this time, the hormone-independent cells eventually become strong enough that hormone therapies will have less and less of an effect on the growth of the tumor. However, because the hormone-sensitive cells aren't actually eradicated, a number of “secondary” hormone approaches can be used to keep the tumor from spreading.

For many men who were using an antiandrogen in combination with an LHRH agonist, stopping the antiandrogen, or *antiandrogen withdrawal*, is the most common first step in secondary hormone therapy. *Switching* to a different antiandrogen might also be able to

offer an extra few months of benefit before other therapeutic approaches are required.

Another option is to block the release of testosterone from the adrenal glands, small organs that sit on top of the kidneys. Only about 10% of the circulating testosterone is produced by these two glands, so few therapeutic interventions focus on them until it becomes important that every last bit of the hormone is removed. The two most commonly used drugs used for this purpose, *ketoconazole* or *aminoglutethimide*, are typically administered in conjunction with steroids to avoid the effects seen when the adrenal glands are shut down.

As a final option, *estrogen therapy* can be added to the mix. A synthetic form of estrogen known as diethylstilbestrol (DES) was the first hormone therapy used in lieu of surgical castration, but was removed from the market because of safety issues in women who were taking it to prevent miscarriage. Nevertheless, it continues to be used for men with prostate cancer, and can be obtained from non-US pharmacies or can be synthesized from other estrogens. Although the drug has proved to be effective in counteracting the effects of testosterone and in slowing the growth of prostate cancer, continuous estrogen therapy has been associated with increased cardiovascular side effects including blood clots and strokes, and is therefore often administered along with an anticoagulant drug.

Other estrogens might be used when DES is unavailable, but all have the same side effects. Because estrogen is one of the main hormones that affect female characteristics, signs of demasculinization such as increased breast size and tenderness, are commonly seen. Importantly, many plant-based and complementary medicines can have estrogen-like properties and can interfere with the effectiveness of your hormone therapy, so be sure that your doctor has a complete list of all drugs — including the “non-traditional” ones — so that he or she can better monitor the effects of your therapy on the progression of your disease.

Deciding on a Course That’s Right for You

The many options for hormone therapy make it difficult to know how and when to proceed. But regardless of which option you

choose, you should feel confident that there's no right or wrong choice. For the most part, it is clear that hormone therapy is essential in men with documented metastatic prostate cancer, particularly if they have symptomatic disease. Other uses of hormone therapy have their pros and cons, and their potential benefits in each case must be weighed carefully. Yet regardless of which regimen is chosen and how it is used, all hormone therapy strategies work toward the same goal of slowing the growth of your prostate cancer.

For most men, the hardest part of hormone therapy is the side effects. The presence of testosterone is important for those characteristics that we typically associate with masculinity; the feminization seen with its loss — even if estrogens are not added — can be difficult for many men. Carefully review the side effect profile of the different regimens, and discuss with your healthcare team potential ways to minimize the effects. In the end, it's important that you not only understand the value of the therapy in the management of your prostate cancer, but also that you learn how to live your life as best as possible while fighting the disease.

CHAPTER 7

The Role of Chemotherapy

When most people think of treatments for cancer, three things come to mind: surgery, radiation therapy, and chemotherapy. In fact, in nearly all cancers, chemotherapy is a mainstay of treatment, and is often one of the first options employed.

However, this has not been the case for prostate cancer, and, until recently, chemotherapy was used only to relieve symptoms associated with very advanced or metastatic disease. With the publication of two studies in 2004 showing that the use of docetaxel (Taxotere) can prolong the lives of men with prostate cancer that no longer responds to hormone therapy, more and more doctors are recognizing the potential benefits of chemotherapy for the men they treat with advanced prostate cancer.

As we discussed in Chapter 6, in earlier stages of prostate cancer, most of the cells are sensitive to changes in testosterone. And, because a primary goal of all cancer therapies is to interfere with the growth of cancer cells as directly as possible, drugs that target testosterone are employed first. But as the cancer progresses and the hormone-independent cells start to take root, therapies that can control the growth of or kill these types of cancer cells as well become important players in the fight against this disease.

Therefore, it's not surprising that chemotherapy has been used as a treatment option at the latest stages of disease. But it also helps to explain why some researchers are looking at using it in earlier stages — if chemotherapy and other hard-hitting anti-cancer therapies can be used earlier, we might be able to slow the growth of the hormone-independent cells and prolong further the lives of men with prostate cancer.

In this Chapter, we'll look at how the drugs being used and developed today are changing the way we view the role of chemotherapy in the management of advanced prostate cancer.



Understanding Chemotherapy

The term “chemotherapy” refers to any type of therapy that uses chemicals to kill or halt the growth of cancer cells. The drugs work in a variety of ways, but are all based on the same simple principle: stop the cells from dividing and you stop the growth and spread of the tumor.

The first step in cancer cell growth is cell division. Each cell divides into two, each of those two divide into two, and so forth. As the cells continue to divide, they take up more and more space, and ultimately become a tumor mass. The goal of chemotherapy, therefore, is to somehow stop the cancer cells from dividing and the tumor mass from growing.

But stopping the tumor from growing is not enough, because oftentimes the tumor will take up enough space that it will press up against other organs and cause pain or other symptoms that negatively affect quality of life. So when we look at whether a drug is working, there are generally two levels of effectiveness — whether a drug is palliative, meaning whether it can alleviate symptoms, and whether it can affect the tumor’s growth significantly enough to prolong life.

As we touched on earlier, chemotherapy is a mainstay of treatment of a number of cancers. In breast and colorectal cancers, it’s often used in conjunction with surgery and/or radiation to improve the chances of killing all of the circulating cells, and to reduce the odds of the cancer coming back. Perhaps the best results with chemotherapy have been seen in testicular cancer, where the use of chemotherapy cures the disease in the majority of cases.

In prostate cancer, as we noted earlier, chemotherapy wasn’t seen as an essential part of the therapeutic regimen for many years, and was only seen as a treatment of last resort. Things have started to change, and more and more doctors are looking to chemotherapy to help alleviate symptoms and prolong the lives of men with advanced prostate cancer.

More and more doctors are recognizing the potential benefits of chemotherapy in the management of advanced prostate cancer.

The Drugs: What We Use and Why

As we touched on earlier, the benefits of chemotherapy in prostate cancer were only first realized recently: mitoxantrone (Novantrone) was approved by the FDA in 1996 and docetaxel (Taxotere) was approved in 2004. Before these two drugs came along, no treatments had proven beneficial in men who had prostate cancer that was no longer responsive to hormone therapy. The availability of these drugs changed the way that researchers looked at chemotherapy and how it might be able to affect the lives of men with advanced prostate cancer.

In 1999, two clinical trials were started to see if docetaxel could provide a benefit to men with advanced prostate cancer and prolong their lives. By this time, two other clinical trials had shown that mitoxantrone could provide palliative benefit, or pain relief, to men with advanced prostate cancer. Once the results of the earlier trials became known, mitoxantrone was established as the “standard of care,” or the accepted practice by doctors across the country when treating men with symptomatic prostate cancer.

The two docetaxel trials were designed somewhat differently from one another, but the goal of both trials was the same: to see if docetaxel can work at least as well as mitoxantrone, if not better. When the results were published in 2004, the trials showed that docetaxel prolonged the lives of the men who took it as well as relieved symptoms better than mitoxantrone.

The men who took docetaxel in these two trials lived for an average of two to three months longer. But many men saw prolonged benefits, and because most men at this stage of disease tend to have a shortened life expectancy, even those who didn't were glad to have gotten even that short amount of extra time with their families and friends. Importantly, researchers looked at the results of these two trials as an important signal that if one chemotherapy drug could prolong the lives of men with metastatic hormone-refractory prostate cancer, other drugs might be able to match it or even surpass it.

At this time, there are dozens of clinical trials studying various combinations of chemotherapy drugs, some using new mixes of older drugs and some using newer drugs. Some trials are looking to find a chemotherapy regimen that's more tolerable or more effective

than docetaxel in men with metastatic disease, others are looking to find a chemotherapy regimen that can delay the onset of metastases, and still others are seeking to improve upon the results with docetaxel by adding to it other novel agents and testing the combination. Unlike what was thought just 10 years ago, there's now little question in the minds of researchers whether we will find something that works even better than what we've already seen — it's now just a question of when.

Using “Off Label” Chemotherapy Drugs

Strictly speaking, only mitoxantrone and docetaxel have been approved by the FDA for use in prostate cancer. But over the years doctors have found that some medications that are regularly used in other types of cancers can be used rather effectively in men with prostate cancer, so you shouldn't be surprised if your doctor suggests a course or two of a different drug on an *off label* use.

Off label use of a drug means that the drug is approved by the FDA for use in one disease but is being used in another. The drugs are known to be safe overall, and have been proven effective for the disease in which it's approved. That doesn't mean it's not effective in prostate cancer as well; in fact, you might find it to be very beneficial. It just means that the drug hasn't been rigorously tested in prostate cancer, so there's no formal “proof” that it's effective. It also means that your insurance carrier might not reimburse you for its cost, so be sure to check into the costs when discussing this option with your doctor.

Getting the Maximum Benefit From Your Chemotherapy Regimen

Most of the chemotherapies available today are given intravenously — the liquid drug is introduced into your body through a needle inserted into a vein. Unlike the pills we're used to taking, such as aspirin or even blood pressure medications, which come in standardized dose and schedules of 10 mg, 250 mg, once a week, and three times a day, the dosing schedule for chemotherapy drugs varies from person to person depending on your weight and height, stage of disease, and a host of other factors.

It's pretty common for a few drugs to be used together. Although they're all designed to slow or stop the growth of cancer cells, each one tends to work in a slightly different way, and using two or more together or one after another in a row can often be more effective than just using one drug alone. You might receive one drug on one day and another drug three days later, or you might receive both on the same day and have to wait an hour in between. The exact dosing schedule will be carefully laid out by your doctors and nurses to ensure that you're getting the most effective treatment possible.

It's ok if you don't understand — or don't care to understand — how and why your doctor chose a particular treatment regimen for you. But you will need to pay careful attention to the instructions given to you by your doctor, nurse, and/or pharmacist about when to come into the office for a treatment, when and how to take any portion of the regimen that might be in pill form, and, most importantly, what sorts of side effects you should look for and when it might be time to call your doctor's office for help. Side effects from some chemotherapy drugs can take a toll on many people. This is not a time to be brave or to ignore warning signs that something might be bothering you. Your doctors, nurses, and pharmacists want you to get well, but they can't help you unless you keep them up to date on how you're faring.

Dealing With the Side Effects of Chemotherapy

The benefits of using powerful drugs to kill your cancer are clear: the stronger the drug, the more likely it will do its job effectively. But there's a downside to this as well: the stronger the drug, the more likely it will also kill normal, healthy cells in its quest to find your cancer cells. Fortunately, unlike the normal cells, which recover over time, the cancer cells have a much harder time growing back.

Each of the drugs available today works in a slightly different fashion, and it's hard to predict what sorts of side effects any one person will experience. But there are a few rules of thumb when it comes to chemotherapy that you should always keep in mind.

- 1) Ignore what other men have told you about their reactions to the different drugs. The dosage that you get might be completely different than what they got, the combination of drugs that you

get might be completely different than what they got, the way you respond to the drugs might be completely different — you get the picture. No two people are the same and no two cancers are the same, which means that no two people will react to the drugs in the same way.

- 2) Pay close attention to *your* reactions to the different drugs. Your doctors, nurses, and pharmacists will tell you what to look out for in general, but that doesn't mean you won't experience something that they didn't anticipate. You're the only one who really knows your own body, so you're the only one who can know when something's not right. Don't worry about being a pest if you call with questions or concerns. It's far better to be extra cautious than to ignore something that might be causing you harm.
- 3) Don't be "macho." There are plenty of drugs available to help ward off or treat the different side effects. If your doctors and nurses give you prescriptions for anti-nausea pills, fill the prescription and use them. If you're having trouble sleeping or are feeling weak and exhausted, work with your health care team to do something about it. All treatments work best when your body is at its strongest. It's your doctor's job to be sure the chemotherapy is fighting your cancer — and it's your job to stay as healthy and strong as possible.
- 4) Focus on yourself. Chemotherapy drugs are powerful and can take a toll on your body. This is a time for you to focus on what you need to do to make you well. Find something that helps you relax — listening to music, doing yoga or stretching exercises, taking a walk in the woods or on the beach, or watching a movie marathon on television. It doesn't matter what you do, as long as it can help you relieve stress and can help you with the most important part of your cancer treatment — getting well.

Finally, keep in mind that chemotherapy might not be appropriate for everyone. Although many of the side effects are temporary, it can take toll on your body, increasing your risk for infection and causing fatigue. Therefore, when deciding about whether chemotherapy is right for you, your doctors will evaluate how strong

and healthy you are, and determine how well you are likely to tolerate the treatment regimen.

What if the Chemotherapy Doesn't Work?

When the chemotherapy is working, some men might find symptom relief, while others might find that their metastases have shrunk. But nearly all men will show a drop in their PSA levels, which is why the PSA level is used as an important indicator of whether the chemotherapy is doing its job.

When chemotherapy is working, PSA will drop in nearly all men, making it an important indicator of whether the chemotherapy is doing its job.

But remember that no two cancers are the same and no two people react to chemotherapy drugs in the same way. So if your PSA doesn't fall, if you don't find symptom relief, or if your metastases don't stop growing, don't be discouraged.

You might just need to start on a different type of drug or combination of drugs to see a better result.

Because very few drugs will score a home run in every person, *second-line chemotherapy* has a long and valued tradition in the treatment of cancer. They're not second-rate drugs; in fact, they might be the drugs that other men are using first. The important thing is that the second-line drug works somewhat differently than the first, so you've got another chance to see a benefit.

In the end, you might find yourself using two, three, or even four different chemotherapy drugs over the course of your disease. You might join one or more clinical trials to see if a new drug regimen works well, and you might obtain small benefits at each step of the way. The key is to stay focused on staying strong and to work with your healthcare team to find the treatment path that's right for you.

CHAPTER 8

Managing Bone Metastases and Pain

As cancer cells begin to spread outward from their original starting place, they can spread locally, to the immediately surrounding areas, or they can spread distantly, to other organs in the body. There's no way to predict exactly how any type of cancer will spread, but, over the years, researchers have found that different types of cancers tend to spread in distinct patterns, and that different types of cancer cells seem to prefer to settle in some areas more than others. For reasons that remain somewhat unclear, prostate cancer cells seem to prefer bone tissue and tend to migrate there after escaping the pelvic region.

Once the cells settle in, they're known as prostate cancer *bone metastases* (singular is *metastasis*). Unlike bone cancer, which originates in the bone, prostate cancer bone metastases are actually collections of prostate cancer cells that happen to be sitting within the bones. Therefore, the same treatments that are used to kill prostate cancer cells in other areas, such as hormone therapy and chemotherapy, are often used in men with bone metastases as well.

But the prostate cancer cells in the bone don't just sit there idly. They interact with the bone tissue, often disrupting the normal growth and function of the bone and weakening it. So in addition to any traditional anti-cancer treatments that your doctors might have already given you, treatment strategies for bone metastases also have to focus on making sure that your bones stay as healthy and strong as possible.

Ultimately, there are three treatment goals for men with prostate cancer bone metastases. As with all anti-cancer treatments, the first goal is to slow the growth of the cancer cells as best as possible. The

Unlike bone cancer, which originates in the bone, prostate cancer bone metastases are collections of prostate cancer cells that happen to be sitting within the bones.



second is to reduce the complications caused by the metastases and the weakened bone tissue. But the third and equally important goal is to relieve or prevent pain. Many men with prostate cancer bone metastases experience pain, and dealing with untreated pain expends a lot of energy — energy that you need to stay healthy and strong.

In this Chapter, we'll review some of the more common problems caused by bone metastases as well as the ways that doctors and researchers have learned to treat the metastases and improve the lives of men with advanced prostate cancer.

Detecting Bone Metastases

Because the prostate is sitting in pelvic region, that's often the first area to which the cells will travel: the pelvic bone, the lower spine, and the upper thighs. For many men, pain in this region is often the first sign that the cancer might have spread to the bone or that there might be a complication from a bone metastasis. Some might experience constant pain localized to a particular area, while others might experience bursts of pain in a number of different areas that wax and wane over time.

If your doctor suspects that the pain might be due to a bone metastasis, or if your doctor feels that you are at high risk of developing a metastasis, you will likely undergo one or more tests to determine the size and location of the metastasis. The “gold standard” test, or the one that is considered the best, is the bone scan, or bone scintigraphy. A radioactive substance that acts like a dye is injected into your vein, and images of your entire skeleton are taken. When prostate cancer cells settle in the bones, they don't just sit there. They interact with the bone cells, causing new bone cells to grow and causing the bone tissue to break down. The dye-like material that's injected highlights areas of bone metabolism or activity — areas where bone tissue is changing more rapidly than it normally would in a healthy adult male.

Bone scans are very *sensitive*, meaning that they can detect even small amounts of increased bone metabolism. But they're not very *specific*, meaning that the changes they detect might not be caused by prostate cancer bone metastases. In fact, the dye might be detecting changes in the bone due to a previous fracture, infection, arthritis, or

even bone loss that can result from the use of hormone therapy.

This is another reason it's important that all of your doctors have a complete record of your medical history. Treatments for bone metastases can be very effective, but they're not appropriate for other diseases or disorders that can damage your bones and joints. Knowing your complete medical history can help your doctors better assess the results of your bone scan and therefore determine the treatment approach that's right for you.

Also, keep in mind that even if your treatment is effective at controlling the growth of bone metastases, you might not see a change on a new bone scan. Your doctors might use other types of scans, such as x-rays, CT scans, MRIs, and PET scans, to monitor the effects of the metastases over time and to determine whether any new changes on a bone scan are caused by bone metastases.

Treating Bone Metastases

There are a few different kinds of treatments for prostate cancer bone metastases. Because they all work in different ways, your doctors might choose to use more than one in your treatment regimen. That doesn't mean your metastases are harder to treat or that your prognosis is worse. All it means is that your doctors want to be sure that they will be able to help keep your bones as strong and healthy as possible.

Before beginning any treatment regimen for bone metastases, your doctors will likely discuss with you the importance of maintaining a healthy diet and lifestyle. They will want to ensure that you're taking in adequate amounts of calcium and vitamin D, and that you're exercising regularly. Even though none of these are treatments for bone metastases, they will all help you maintain strong bones and help to minimize bone loss and osteoporosis, which can make treating your bone metastases more challenging.

Men who experience pain from a bone metastasis will often be treated with radiation targeted directly to the metastasis. This will kill the prostate cancer cells that are sitting there and thereby relieve the pain. Note that the goal of radiation therapy that is used to treat bone metastases is completely unrelated to any radiation that you might or might not have received earlier in your prostate cancer treatment. Regardless of whether you had surgery, radiation, chemotherapy, or

any other type of treatment up until now for your prostate cancer, radiation to the bones can be used to relieve the pain from bone metastases.

External beam radiation therapy uses x-rays to kill the cancer cells sitting in your bones. This type of treatment, sometimes referred to

Regardless of whether you had surgery, radiation, chemotherapy, or any other treatment, radiation to the bones can be used to relieve the pain from bone metastases.

as *spot radiation*, is mapped out and planned very precisely by the radiation oncologist to ensure that the x-rays are targeting the metastasis and are not causing damage to the surrounding bone and muscle tissue. A procedure known as *hemi-body radiation*, which is used less frequently, targets

much larger areas of the lower half of the body, which is where prostate cancer bone metastases more typically grow.

A somewhat different approach uses *radiopharmaceuticals* to target the bone metastases. These radioactive drugs, either samarium (Quadramet) or strontium (Metastron), are injected into your body through a vein and settle in the bone metastases, at which point they release radiation to the local area and kill the cancer cells. Researchers have shown that strontium can be very effective at relieving pain when used immediately after the chemotherapy drug doxorubicin (Adriamycin), so your doctors might decide to combine the two approaches in an attempt to give you the most relief possible.

External beam radiation therapy and radiopharmaceuticals are known as *directed palliative* treatments, meaning that they are used to relieve pain in a specific area of the body. Drugs known as *bisphosphonates* are systemic therapies that have been shown to relieve pain throughout the body and to slow the onset of complications from bone metastases in men with prostate cancer.

Under normal circumstances, bone cells are destroyed and created at a constant rate. Increasing the activity of *osteoblasts*, cells that form new bone cells, ultimately results in an overgrowth of bone tissue; increasing the activity of *osteoclasts*, cells that destroy bone cells, ultimately results in porous, brittle bone tissue. In men with prostate cancer bone metastases, both of these processes occur at faster than

normal rates, leading to both an overgrowth of bone tissue and weakened and brittle bones. The combination of these two processes makes the bones unstable, and therefore prone to fracture.

Bisphosphonates are drugs that are designed to help reset the balance in the bone between bone growth and bone destruction. Zoledronic acid (Zometa) is a bisphosphonate given intravenously that can delay the onset of complications associated with prostate cancer bone metastases and relieve pain. It is typically given once every three weeks as a 15-minute infusion. Another intravenous bisphosphonate known as pamidronate (Aredia) is less frequently used, and has been shown to have limited benefit in this setting.

Many men feel flu-like symptoms after the first few infusions of zoledronic acid, including fatigue, nausea and vomiting, and generalized aches and pain, but they usually fade within a few days. Also, the drug can cause kidney problems in some men, so your doctor might take some blood before each infusion to make sure that your kidneys are working properly.

Finally, be sure to tell your dentist that you're taking zoledronic acid before you have any sort of dental surgery. The bone tissue in your jaw can be affected by the drug, and removing a tooth or having some other kind of procedure that requires your dentist to cut into your jaw can cause some additional damage to the bone. Remember: It's important that all of your doctors have a complete record of your medical history, especially a list of all medications and supplements that you might be taking, so they can know how best to help you.

Other bisphosphonates are sometimes used in men with prostate cancer to prevent or slow bone loss while taking hormone therapy. These drugs, alendronate (Fosamax) and risedronate (Actonel), are given in pill form, and are also used to counteract the bone loss of osteoporosis in postmenopausal women or in women who are taking hormone therapy for breast cancer. If another doctor started you on a bisphosphonate to help fight off bone loss from hormone therapy, be sure to tell your oncologist. It's important that all of your doctors and nurses have a complete list of the medications you're taking so they can know how best to help you.

Because bone metastases affect so many men with prostate cancer, researchers are working hard to find new therapies that can min-

imize the pain and complications resulting from the metastases. Most of these new drugs work by blocking the prostate cancer cells from interacting with the bone tissue, with the hope of slowing or preventing the development of bone metastases and thereby improving the outcomes in men with prostate cancer.

Anticipating Complications From Bone Metastases

As we noted earlier, treatment for prostate cancer bone metastases has three goals: to slow disease progression, to relieve pain, and, perhaps most importantly, to avoid the complications that stem from the weakened bone caused by the metastases.

Pathologic fractures are bone fractures that are caused by disease. Bone that is weakened by metastases is more prone to fracture, and because the metastases often grow around the lower back and upper legs, hip fractures tend to be most common. If you already have some bone loss from hormone therapy or from other causes, your doctors will likely be vigilant about monitoring for fractures, so be sure to report any falls that might precipitate a pathologic fracture. Also, your doctor might discuss with you the possibility of undergoing surgery to stabilize the bones at risk. This can improve your chances of not fracturing the bones, and therefore help to stave off other complications down the road.

By far, the most significant complication from bone metastases is *spinal cord compression*. The delicate spinal cord runs from the base of your brain down your spine deep inside the *vertebrae*, the bones that comprise the spinal column. The spinal cord houses most of the nerves that control movement and activity in your body, and damage to your spinal cord can result in permanent disability. Therefore, the vertebrae (singular is *vertebra*) have to stay very strong in order to protect the spinal cord.

The vertebrae are stacked one on top of the other. A weakening of a vertebra by a prostate cancer bone metastasis can result in the bones collapsing one on top of the other, compressing the spinal cord and the nerves that run out from it.

Cord compression associated with metastatic prostate cancer can cause severe nerve damage, and possibly paralysis, if not managed immediately. Therefore, if your doctor feels that you are at high risk

for a spinal cord compression, you might be placed on additional medications, such as steroids, to counteract the effects that might occur should it happen, or you might be considered for a surgical procedure to stabilize the weakened bones. You also might be sent for MRI scans to better visualize the health of your spinal column and to detect early any problems that might occur.

Note that the symptoms of spinal cord compression can be subtle, and might be similar to those seen with many other medical problems. For example, because bone metastases typically occur around the lower back and upper legs, compression of the spinal cord at that point can cause back pain, leg pain or weakness, or loss of bladder or bowel control.

Since you're the only one who really knows your own body, you're the only one who can know when something's not right. Don't assume that any pain that you're having is normal, or that any change in your bowel or bladder habits are "just another side effect." They can be signs of a more serious problem, so be sure to tell your doctors about any changes you see. The earlier you can detect any new fractures or a spinal cord compression, the easier it is to treat.

Managing Pain

Although pain can oftentimes be relieved by treating the bone metastases with radiation, bisphosphonates, or other bone-targeted therapies, you might still need additional pain medications.

There are three general rules of pain management that you should always keep in mind.

- 1) Don't try to be too tough or act "macho". Cancer can be painful, and there's no benefit in acting stoic and pretending it doesn't affect you. Untreated pain takes a toll on the body, forcing it to expend a lot of energy fighting it. There are plenty of very effective pain medications available, and using them will allow you to feel better and stay stronger.
- 2) There might be a very simple solution to your pain. Don't assume that you can't get pain relief unless you're completely doped up. Remember, the goal of pain management is to keep your body strong so you can fight your disease. Some very

simple and easy to take oral medications might be enough to ease your pain and help you get back on track.

- 3) Don't worry about becoming addicted to pain medication. The most common reason that doctors are afraid to prescribe strong pain medications and that people are afraid to take them is fear of addiction. But that's mostly because people don't understand the differences between addiction, physical dependence, and tolerance.

Addiction is a psychological and behavioral syndrome in which there is continual or increasing use of a drug despite negative physical, psychological, or social consequences. In fact, taking pain medications so that you can spend your days feeling healthier and stronger would seem to be exactly the opposite of addictive behavior.

On the other hand, both physical dependence and tolerance are possible, so you and your doctors should take them into consideration as you start and stop different pain medications.

If you are *physically dependent* upon a drug, your body will not know how to cope with its loss if you stop it or lower the dose too rapidly, and you will show symptoms of withdrawal. This is why doses of strong pain medications are usually *tapered* before stopping, meaning that your doctors will give you a gradual lowering of the dose over time so that your body will learn to adapt and adjust to its loss.

If you use a certain drug for a long period of time, you can build up a *tolerance* to it, to the point where the drug is no longer effective. Slowly increasing the doses over time can help to avoid the onset of tolerance, but that's only a temporary measure, and you'll likely have to switch to a medication that works in a slightly different manner before you can find relief.

Keep in mind that if you have a history of drug addiction or drug abuse, you should tell your doctors as soon as possible. It won't keep you from getting any pain medication, but it will ensure that your doctors monitor your responses to your medication more closely so you don't get too physically dependent or build up a tolerance too quickly. In addition, it is likely that you will need higher doses of the medication to gain the full benefit and overcome your tolerance to the medication.

If your doctors seem unwilling or unsure of how to treat your

pain, seek out the opinion of a pain specialist. There are dozens of different types of medications available, some designed specifically to treat long-term pain and some designed specifically to treat brief pain flares. If you find no relief from oral or intravenous drugs, there are also a number of minor surgical procedures that can be done to help you find relief.

Keep in mind that every pain medication, like all other medications, has its own set of side effects. Constipation is the most common side effect of pain medication use; so common, in fact, that it is not a question of *if* you will be constipated, but

rather a question of *when* you will get constipated. If you use pain medications on a regular basis, even as little as once a day, you will need to start on an aggressive bowel regimen with stool softeners, laxatives, or other therapies to prevent constipation and the problems that can result from it if not treated effectively.

Other side effects can include nausea and vomiting, sleepiness, and confusion. Most of these start to fade as your body builds up tolerance to the drug, but be sure to discuss the side effects with your doctor so you can know what to expect and how to deal with it.

Remember, your goal is to stay as strong and healthy as possible so you can fight your disease. It might take some time to figure out how to effectively treat your pain, but if you work with your team of doctors and nurses, together you will find the treatment path that's right for you.

There are plenty of very effective pain medications available, and using them will allow you to feel better and stay stronger.

CHAPTER 9

Emerging Therapies on the Horizon

Until now, we've been talking about treatment options that are regularly used for men with prostate cancer and how doctors have been working to optimize delivery of these drugs and improve outcomes in men at all stages of disease.

But in labs around the world, researchers are busy identifying new drugs, new regimens, and new treatment approaches that might prove beneficial to men with prostate cancer. As we'll see, the process from lab to clinic is long and arduous, and not all drugs that seem promising in the lab end up working quite as well in people. Nevertheless, the potential ability to identify a new drug therapy that can help men live longer or have better quality of life even for a short amount of time is enough for these dedicated researchers to continue in their quest to find better treatments for prostate cancer.

Most of the investigational agents that we'll review in this Chapter are being tested in men with advanced prostate cancer. Therapy options for men at this stage of disease are often not effective enough to halt progression of the disease, and men are typically affected by side effects from the disease and/or the medications that they're taking. It's therefore the perfect stage at which to test out new drugs because any improvement will likely be rapidly noticed and much appreciated.

Ultimately, however, none of the agents currently being investigated can ever come to benefit men with prostate cancer unless rigorous clinical trials are conducted. As you read through this Chapter and learn about new agents on the horizon, remember that none of the research would be possible without the help of the thousands of men who enrolled in clinical trials and joined the researchers in the fight against prostate cancer. (For more information about whether enrolling in a clinical trial might be right for you, turn to Chapter 10.)



The Goal of Targeted Therapies

Chemotherapy drugs can play an important role in improving the lives of men with advanced prostate cancer, but they often don't dis-

tinguish between tumor cells and healthy cells and can kill off some normal cells along the way. So-called *targeted therapies*, by contrast, are drugs that are specifically designed to interfere with the way cancer cells grow, with the way cancer cells interact with each other, and/or with the way that our bodies' immune systems interact with the cancer.

There are a number of different kinds of targeted therapies being investigated for prostate cancer; in this Chapter, we'll focus on four of them. Some of the drugs in these four categories have shown promise in the lab and are only first starting to show benefit in men

with the disease. Others are already being rigorously tested in men enrolled in large clinical trials and look like they might provide significant benefit to men with advanced prostate cancer. As of yet, none of these drugs have been approved by the FDA for use in prostate cancer, but the excitement generated by some of the early studies have led many researchers to believe that it's only a matter of time before a targeted therapy is found that can result in better outcomes overall.

Targeted therapies interfere with the way cancer cells grow and interact with each other or with the way that our immune systems interact with the cancer.

Interfering With Cancer Cell Growth

All cells in the body, including cancer cells, rely on a complex communication system to know when to grow, when to divide, and when to die. This system uses specialized proteins, fats, and other substances to tell the different cells or parts of cells how to act. For example, when cells in the pancreas detect an increase in sugar in the blood, they produce a protein called insulin. The release of insulin, in turn, signals other cells to start breaking down the sugar into smaller components so that its nutrients can be absorbed by the body.

Over the years, cancer researchers have been studying ways to interfere with the signaling system that regulates the growth of cancer cells. In the same way that jamming a radio signal prevents transmission, jamming the cancer cell's communication system can stop

it from functioning and therefore stop the cancer from growing. But because the system uses dozens of different signals at different times to stimulate different steps in cancer cell growth, the challenge is to find the one spot along the way that, if disrupted, can grind the entire process to a halt.

Suppose a cancer cell was getting ready to grow. A receptor built into the cell's outer wall would pick up a *growth factor*, or a specialized protein that stimulates the cell to start the process. The receptor would read the instructions in the growth factor and pass them along to another part of the cell so the instructions can be carried out. But if the receptor could be prevented from picking up the signal or from transmitting the message to the rest of the cell, the entire process would shut down and the cell would be blocked from growing.

Drugs that *inhibit*, or block, the activity of growth factor receptors is one type of targeted therapy being studied in the treatment of cancer. So far, only a few have made it from the lab to the clinic: imatinib (Gleevec), which is used in a type of leukemia known as chronic myeloid leukemia or CML, and erlotinib (Tarceva), which is used in lung cancer.

Imatinib was one of the first of the so-called targeted therapies to be approved by the FDA for the treatment of cancer, and has been shown to be very effective in stopping certain types of leukemia cells from growing. It is currently being tested for use in other types of cancers, including prostate cancer. Although early studies showed that imatinib alone wasn't too effective in stopping prostate cancer cell growth, fairly significant drops in PSA were seen when imatinib was added to the chemotherapy drug docetaxel (Taxotere). Larger clinical trials are now being conducted to see if the combination of the two drugs is more effective at halting cancer cell growth than just using docetaxel alone.

So far, interfering with cellular signaling to halt cancer cell growth hasn't yet proven to be a very effective strategy in prostate cancer. But, as we'll see below, the strategy of adding a targeted therapy to other effective drugs in order to see better results than with either drug alone has become an important part of cancer research. The idea is to exploit the *synergy* between the two drugs, or the ways in which the two drugs might work together to fight off the cancer.

Interfering With Cancer Cell Spread

Cancer cells, like all cells, are living organisms that need a constant supply of nutrients to survive. In the body, nutrients are delivered to cells through the bloodstream. In fact, if the blood supply to a part of the body is cut off, the cells slowly start to die.

As cancer cells divide and start to spread, new blood vessels sprout from the old ones to help supply the necessary nutrients to the new tumor site. This process is called *angiogenesis* (*angio*, meaning blood vessel; *genesis*, meaning beginning). If angiogenesis could be inhibited, theorized researchers, the new tumor cells would die and the cancer's growth would be halted.

In 2004, the angiogenesis inhibitor bevacizumab (Avastin) was approved by the FDA for use in colorectal cancer. Since then, it has been shown to improve outcomes in women with breast cancer, and is currently being studied in a number of other cancer types, including prostate cancer. Here, too, the *synergy* between two agents is being tested, and a large clinical trial is now underway to see whether bevacizumab plus docetaxel would be more effective at stopping cancer growth than docetaxel alone.

Although no other drugs currently available were designed to specifically act as an angiogenesis inhibitor, researchers have found that the drug thalidomide (Thalomid) has some anti-angiogenic properties, and is currently being tested in men with prostate cancer.

Thalidomide was originally developed in the 1960s to treat morning sickness in pregnant women. It was quickly pulled from the market, however, after it was found to cause severe birth defects in the children of those who took the drug, resulting in about 8,000 children being born with malformed, shortened limbs. Interestingly, researchers now know that one of the reasons thalidomide caused the birth defects was because of its anti-angiogenic properties — the drug was typically taken just as the arm and leg buds were starting to grow in the fetus, and effectively prevented them from forming normally.

Exploiting the synergy between two drugs, or the ways in which they work together to fight off the cancer, has become an important part of cancer research.

Thalidomide was subsequently approved for use in people with Hanson's disease, or leprosy, and has been used successfully off-label in a type of blood cancer known as multiple myeloma.

Early studies of thalidomide alone in men with prostate cancer showed it to be only marginally successful at slowing the cancer's growth. But when combined with docetaxel, it proved far more effective. Additional studies are being conducted to see whether the combination of the two would be more effective than docetaxel alone. Newer types of thalidomide-like drugs are also being tested, and so far have shown some promise as well.

Interfering With Activity of Cancer Cells in the Bone

Under normal circumstances, bone cells are destroyed and created at a constant rate. Stepping up the activity of *osteoblasts*, cells that form new bone cells, ultimately results in an overgrowth of bone tissue; stepping up the activity of *osteoclasts*, cells that destroy bone cells, ultimately results in porous, brittle bone tissue.

When prostate cancer starts to spread outward from the pelvic area, it almost always settles first in the bone. The growth of prostate cancer in the bone, known as *prostate cancer bone metastases*, can result in pain and fractures in some men. (Treatment options for bone metastases and bone pain are discussed in Chapter 8.)

Once the cancer cells reach the bone tissue, among the proteins that they produce is a protein called endothelin. This protein steps up the activity of osteoblasts, producing additional bone cells. Formation of these cells, in turn, stimulates the growth and spread of prostate cancer cells, bringing us right back around again to where we started.

As we discussed earlier, the first step in transmitting instructions to a cell is for the cell's receptors to read them. If the endothelin receptor could be blocked, researchers theorized, the cycle would be halted, and disease progression in the bone could be delayed.

The drug atrasentan (Xinlay) blocks the receptor that reads endothelin's instructions. Studies of the drug in men with bone metastases showed that it can slow the progression of prostate cancer and can delay the onset of bone pain. Researchers are now focusing their efforts on determining whether blocking endothelin's

receptor in men with very early stages of advanced prostate cancer can prevent the growth of bone metastases.

At the time of this writing, atrasentan is being evaluated by the FDA for possible approval. Even if it doesn't get approved at this time, many researchers are optimistic that they will identify a way someday soon to stop the action of endothelin and thereby relieve the many problems associated with the development of bone metastases in men with advanced prostate cancer.

Harnessing the Immune System to Fight Off Cancer Cells

Your body's immune system is designed to fight off invading cells that it thinks might harm you. In fact, each day, your immune system might detect and destroy dozens of microscopic bacteria and viruses. Unfortunately, it's not quite as efficient when it comes to fighting off cancers.

Because your body only wants to fight off foreign invaders, it has to learn to recognize what's normal and what's not normal. For example, when you're first exposed to a virus that causes the common cold, your body doesn't know what it is, so you experience the full course of symptoms. Once it clears up, however, your immune system remembers what the virus looked like, and, if exposed to it again, knows how to fight it off. Unless your immune system is somehow impaired, this process works fairly well, and helps you stay healthy most of the time. Note that the fact that you can catch a cold again doesn't mean there's something wrong with your immune system; it means that you were exposed to a different cold virus.

Cancer cells start out as normal healthy cells. Even though, over time, they become more and more disorganized and start looking less and less like normal cells, the immune system never has a chance to learn to distinguish between the normal cell and the cancer cell. Your immune system isn't incapable of fighting off the cancer cells — it just doesn't know that it's supposed to.

As we noted above, the only way that your immune system can learn to fight off a new invader is for it to be exposed to it. But there are some bacteria or viruses that, if exposed to them just the one time, can be life threatening. For this reason, researchers have devel-

oped *preventive vaccines* to teach the body how to fight the invader. Preventive vaccines might contain a weakened virus, a killed whole virus, just a small part of the virus. The idea is to get your body to develop a way to fight it off should you come into contact with the virus again.

Few cancers are caused by bacteria or viruses, so, for the most part, developing preventive vaccines for cancer isn't very practical. But *therapeutic vaccines* that stimulate the immune system to recognize and fight certain proteins specific to cancer cells can be effective, and

have been tested in a number of different cancers including melanoma, non-Hodgkin's lymphoma, and prostate cancer.

Each of the therapeutic vaccines currently being tested in men with advanced prostate cancer works in a slightly differ-

Therapeutic vaccines harness the immune system's ability to fight off disease and teach it to fight off prostate cancer cells.

ent fashion, but all are designed to harness the immune system's ability to fight off disease and teach it to fight off prostate cancer cells.

Studies of the therapeutic vaccine *Provenge* have shown it to be most effective in men with advanced prostate cancer who had Gleason scores lower than 8. In this group, the immune system was activated, the cancer cell growth was slowed, and cancer-related pain was relieved. Studies of another therapeutic vaccine, *GVAX*, showed that it, too, might be beneficial in men with advanced prostate cancer, and is currently being evaluated in combination with the chemotherapy drug docetaxel.

As of yet, no therapeutic vaccine has been approved by the FDA for use in prostate cancer or in any other cancer. But researchers are optimistic that therapeutic vaccines might soon prove to be another effective strategy to help slow the progression of disease in men with advanced prostate cancer.

The Future of Prostate Cancer Research

In this Chapter, we've focused on a few of the more promising drugs and targets being studied in prostate cancer. Dozens of other drugs are being studied as well, and early results with a number of these

drugs have shown them to be effective in slowing or stopping the growth of prostate cancer.

Because no two cancers act in the same way and no two men respond to treatment in the same way, the likelihood that any of these drugs will eradicate prostate cancer completely is pretty low. Instead, most researchers are hoping that the drugs will help men with advanced prostate cancer live better and longer lives, allowing them to spend less time dealing with the problems caused by their disease and spend more time enjoying life with their families and friends.

CHAPTER 10

Participating in Clinical Trials

The process of moving a new cancer therapy from the lab to the clinic can be long and difficult, and for every therapy that makes it through, there are many, many more that don't. What holds things up? Why is it so difficult to get good, effective therapies into the hands of people who need them?

The United States Food and Drug Administration (FDA) is tasked with ensuring that all of the drugs that we use — from Tylenol to Taxotere — are as safe and effective as possible. No two people react to a medication in exactly the same way, so there's no way to guarantee that it won't harm someone unexpectedly. And there's no substance on Earth that won't cause some sort of side effect if given to someone who can't tolerate it. Recognizing all of that, the FDA has set up a system that is designed to sift out the better drugs from the worse ones, and to try to make the better ones as safe and effective as possible.

The job of the FDA is to get new therapies into the hands of doctors so they can, in turn, get them into the hands of people who need them. Clinical trials are the process by which researchers and the FDA evaluate experimental new therapies, and then determine who will benefit most from them.

In this Chapter, we'll look at the way that clinical trials are used to evaluate the safety and efficacy of a new cancer therapy, and discuss whether participation in a clinical trial might be a good choice for you.

Keep in mind that the process described here might be somewhat different for therapies being developed for other types of diseases, and non-drug treatments or devices will have their own set of rules and regulations. But regardless of exactly which steps a new drug or device will undergo, the goal is the same: to make sure that they're as safe and effective as possible.



The Phases of Clinical Trial Development

Before a new therapy can be approved for use by the FDA, it goes through three different types of clinical trials in people to determine

whether it is safe, whether it is effective in the disease for which it's being tested, and whether it is at least as good — if not better — than what's already being used. It typically takes up to eight years to go through the three different steps. In some cases, it can take less time, but can also often take much longer.

Before the therapy gets to the point of being tested in people, there can be years and years of *preclinical* work, which tests it *in vitro*, in the lab using cells in a test tube, and *in vivo*, in animals. Although researchers usually have a general idea of how the therapy works based on earlier experience, they often don't know exactly how well it will work against different types of cancers. Animal studies, in particular, can be important, because unlike cancers in humans, cancers in animals can grow very rapidly, so the results of the research can be realized quickly. Preclinical studies are therefore often used to get a better sense of exactly *how* the drug works so the researchers will have more insight into *where* it might work.

Once a new therapy has been shown in the lab to stop the growth of cancer cells or to slow them down, it will be first tested in human in what is known as a phase 1 clinical trial.

The *phase 1* clinical trial for the new therapy will be designed to see whether it is safe in people with different types of cancer. The lab work might have shown that the drug can stop one particular step in cancer cell growth, but that step might be important to the growth of breast, colon, and prostate cancers. So researchers will give the therapy to a group of people with different types of cancers, carefully monitoring its effects on the tumors, and gaining further insight into where it might prove most effective. There are usually 10-20 people enrolled in this type of study, so that just a handful of people have each of the different cancer types being tested.

It is at this phase of clinical development where the dosages of the drug are worked out as well. Figuring out the optimal dose can be tricky: a higher dose might kill more cancer cells, but it might also

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cause more side effects. With any therapy, there's always a trade-off between safety and efficacy, and researchers — and the FDA— know that most people would be willing to put up with some significant side effects if it means that the therapy can beat back their cancer. But striking exactly the right balance between the two is very difficult, and many drugs that don't make it to the clinic ultimately fail because the side effects outweigh the benefit.

Enrolling in a phase 1 trial sounds risky and very experimental, but a new therapeutic regimen will only make it to a phase 1 study if

both the researchers and the FDA believe that there is a good chance it'll be effective in people with cancer.

If the new therapy was shown to be safe and a safe dose is determined, it can move on to the next step. Typically, the *phase 2* trial of the new therapy

would enroll 50-250 people with one type of cancer from different institutions, all of whom would receive the study drug at the dosage that was established during the phase 1 trial. The goal of this step is to determine how effective the therapy is in a particular disease setting, and to get a better sense of its side effects. Although the therapy was deemed safe to move ahead after the phase 1 study, it is assumed that additional side effects will show up when given to a larger group, so the study participants are monitored very carefully to see how they react to it.

If it passes through the phase 2 trial and is shown to be effective at slowing or stopping cancer growth with no or few unexpected or severe side effects, the therapy can move to the next step. The *phase 3* clinical trial is typically the most robust, and can have anywhere from 100 to 1000 people or more enrolled in the study at 10-50 or more institutions. The goal of this trial is to determine whether the new therapy is at least as effective — if not more effective — than the current standard of care.

In some cases, there is no accepted form of therapy for a particular type of cancer, so the new therapy will be tested against *best supportive care*, which might include ensuring adequate fluids, rest, and

Most people are willing to put up with side effects if a therapy can beat back their cancer, but striking a balance between the two can be challenging.

pain medications. This was more commonly seen in the late 1980s and early 1990s. But since then, the drug development process has advanced far enough in most cancers that there is usually at least one therapy or therapy regimen that is considered the standard of care against which any new therapy is tested.

However, if active surveillance is the standard of care, such as when your PSA is rising during hormone therapy but no metastases have been detected, a new therapy might be tested against a *placebo*, an inactive treatment that looks similar to the treatment being tested. The goal of a *placebo-controlled trial* in this setting is to determine whether the new therapy being tested is better than active surveillance.

In order to test whether a new therapy is better than the old, the entire study group is typically divided in half, with one half receiving the new therapy and the other half receiving the old. The rates at which the two study groups respond to the two different drugs are then compared.

Once results from all studies of the new therapy are in, the FDA reviews the data and considers whether the availability of the new drug will improve outcomes in people with cancer.

If the answer is yes, the therapy will be approved, and the *label* or *prescribing information* will be written. The label gives very specific instructions to doctors about how the therapy works and how it should be given, so doctors can know how best to use it. (This is why the use of a drug for a disease other than for what it was approved is known as an *off-label* use — it's not being used as written in the drug's label.)

Because new cancer drugs are so desperately needed, even if the FDA isn't convinced that there is enough evidence of a benefit to warrant approval, it's unlikely that the drug will be tossed out completely. Rather, the FDA will mandate additional clinical trials to better assess its efficacy. For example, a trial for a new prostate cancer therapy might show that it is more useful in men with particular tumor characteristics, like Gleason scores less than 7, or in men with specific clinical characteristics, like age younger than 70. In these cases, the FDA will require additional studies to see whether a particular group of men can be identified as the optimal group to receive the therapy.

Even if the drug is approved, that doesn't mean the testing is over. The FDA might be concerned about a particular set of side effects,

and will therefore mandate that *phase 4*, or post-marketing, clinical trials be conducted. Most often, the results from these studies will result in minor changes to the label, giving doctors more information about the way people react to the therapy and what sort of side effects they should be looking out for.

Not all therapies go through these studies in exactly the same way. There can be a combination phase 1 and phase 2 trial; a phase 2 trial that's designed more like a phase 3 trial and that compares two different therapies in two groups of people; a phase 3 trial in which the two groups are intentionally divided unevenly; a phase 3 trial in which more than one regimen of a new therapy is tested against the old drug; or a phase 3 trial that compares three different therapies against each other. But regardless of how the trials are designed, they all have to prove the same three elements: that the new therapy is safe, that it is effective in the disease for which it's being tested, and that it is at least as good — if not better — than what's already being used.

The therapy approval process

	Preclinical Testing	Phase 1-3 Clinical Trials			FDA Review	Phase 4 Clinical Trials
		Phase 1	Phase 2	Phase 3		
Years	6.5	1	2	3	1-3	
Test Population	Laboratory cells and animals	10-20 patient volunteers	50-250 patient volunteers	100-1000 patient volunteers	Review process/ approval	Post-marketing testing required by FDA
Purpose	Assess safety and biological activity	Determine safety and dosage	Evaluate effectiveness, look for side effects	Verify effectiveness monitor long-term side effects		
Success Rate	5,000 compounds evaluated	5 enter trials			1 approved	

The Ins and Outs of Enrolling in Clinical Trials

Clearly, no new therapy for prostate cancer will ever make it into your doctor's hands if people don't enroll in clinical trials. There would be

no way to prove whether the therapy is safe, whether it is effective, and whether it can help improve the lives of men with prostate cancer. Should you be one of the men who enroll in a clinical trial? What are the potential upsides? And what are the potential downsides?

In general, the best time for you to consider enrolling in a clinical trial is when you know that your prostate cancer is progressing, but you feel well and the best treatment option avail-

able for you remains controversial. For example, suppose your PSA is rising after initial therapy but you have no other signs of advanced disease and you're feeling well. This might be the perfect time to enroll in a clinical trial because the researchers will be able to tell fairly easily whether the drug is affecting your disease progression and how the drug will affect you. The researchers would watch whether your PSA continues to rise or starts to fall, and how long it takes you to develop detectable metastases. The combination of these factors would give them insight into how well the drug is working and whether it might be useful in other men at this stage of disease. Of course, enrolling in such a clinical trial might also allow you to try a new treatment to which you might otherwise never have access, a therapy that might slow your disease and offer some benefit.

Regardless of the specific objectives of the trial, there is much knowledge to gain from every person who enters the trial. Although the researchers conducting the trial will learn a lot more if you stay in the trial for a longer period of time so they can monitor your progression over time, they'll often be able to gather some helpful information from your case even if you get out after only a short time, so you should never feel like you wasted your time and their time if you can't make it all the way through. On the other hand, if you know in advance that you're unlikely to be able to stick with the regimen for one reason or another, discuss with your doctor whether there might be a different trial that's more suited to you. Also, keep in mind that clinical trials are used to evaluate new treatment regimens at all stages of disease, so if you aren't up to joining a trial at one point, that doesn't mean you've lost your chance.

No new therapy for prostate cancer will ever make it into your doctor's hands if people don't enroll in clinical trials.

Who Conducts and Funds the Research?

Across the country, there are dozens of institutions that participate in cancer clinical trials and that enroll men into trials of new prostate cancer therapies. In order to streamline the process of data collection and evaluation, typically one person at one institution will be designated as the *principal investigator*, and he or she will be responsible for ensuring that the process runs as smoothly as possible.

In addition to the principal investigator and the doctors or clinical trial coordinators at each institution who are enrolling people into the trials, there are research nurses, statisticians, lab technicians, and many other people involved in monitoring the effect of the drug, collecting the data, and processing the results.

The costs for running a clinical trial can be high, often millions of dollars. Some of the costs are paid for by the company that manufactures the drug, and some are paid for by the government through grants from the National Cancer Institute (NCI), National Institutes of Health (NIH), the Veterans Administration (VA), or other agencies. Finally, some of the costs are paid for by nonprofit organizations, such as the Prostate Cancer Foundation, that fund research projects. Your insurance carrier, including Medicare, will often cover the cost of the regular procedures and doctor visits that are part of the clinical trial. Be sure to find out before enrolling whether this might be an option for you.

But regardless of who subsidizes the cost, the trials must all go through the same rigorous scrutiny by the FDA to ensure that all necessary steps were followed, that all data were collected and reported appropriately, and, most importantly, that the safety and protection of all people enrolled in the study are being constantly and consistently monitored.

How Can You Find Out About Available Clinical Trials?

If you're interested in finding out more about clinical trials, your first step should be your doctors. They might know of trials that are *recruiting* or looking for men in your local area, and can help you decide which trial might be right for you.

Over the years, in order to help researchers recruit as many appropriate people to their trials as possible, a number of Web sites on the Internet have been developed to catalog the different trials. One site,

www.clinicaltrials.gov, is run by the NCI, and includes trials that are sponsored by the NCI as well as trials sponsored by others. Another site, www.trialcheck.org, is run by the Coalition of National Cancer Cooperative Groups, which is composed of hundreds of cancer centers, academic medical centers, community hospitals, and physician practices that conduct and run clinical trials for many different diseases.

In addition to these registries, there are dozens of smaller clinical trials each year that are run in individual cancer centers or institutions testing new compounds and new regimens. Talk with your doctors and nurses about how best to find a clinical trial in your area so you can work together to find one that's right for you.

Deciding on Whether a Clinical Trial Is Right for You

Your doctors might think you'd benefit from a clinical trial of a new drug, and your family and friends might be excited for you at the prospect of trying out a new drug that might prove beneficial. But is enrolling in a clinical trial right for you?

In order to standardize the data collected, all trials set strict *eligibility criteria*. There might be restrictions on prior treatment regimens, restrictions on the stage and grade of the cancers, restrictions on age or overall health, or restrictions on what other treatments you can take during the trial. Because each of these can affect the way a particular therapy might work, the researchers restrict the trials to those with similar characteristics to ensure, as much as possible, that they'll be able to observe the true effect of the new therapy in men with prostate cancer.

If you are eligible to join, the trial *protocol* or design will specify when and how the researchers will collect the data on your progress. You'll have to have your blood drawn regularly, and have regular visits and checkups. This can usually be done in your doctor's office, but it's possible that you'll have to travel to a separate clinical trial site multiple times over the course of the trial. Also, you'll have to be extra vigilant about reporting any and all side effects you might be experiencing, even if you're not sure whether they're related to the study drug. On the other hand, many people who enroll in clinical trials often feel like they're being monitored more closely because they have more frequent access to their healthcare team.

Finally, if you choose to enroll in a clinical trial, you will be required to give *informed consent* and sign a document stating that you understand the risks and benefits involved and willingly agree to participate. This not only gives the researchers the right to include you in their study, but it also makes it clear that you have the right to pull out of the study at any time without it influencing the way that your cancer is managed further down the road.

There's no right or wrong way to approach the question of whether a clinical trial is a good choice for you. But there is one thing you should always keep in mind when thinking over this issue: Your goal should be to stay as healthy and strong as possible so you can fight off your disease. Take the time to pursue those things that will help you achieve your goal, and avoid those things that might distract you from your goal. The key is to stay focused and to work with your healthcare team to find the treatment path that's right for you.



Report to the Nation on **Prostate Cancer**

A Guide for Men and Their Families

Issues to Consider

Questions to Ask Your Doctor

In the following pages, you will find a set of tear-out sheets and wallet-sized cards for each stage of disease that you can carry with you, summarizing key points to consider and questions to ask your doctors.

These lists are by no means exhaustive, and there might be other points that you want to think about as well. The goal is to help you focus on what you need to know about each stage of disease so you can hold meaningful, regular dialogues with all members of your health care team as you find the treatment path that's right for you.

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What to Consider When You've Been Diagnosed With Early-Stage Prostate Cancer

1. The Gleason grading scale runs from 1 to 5, where 1 represents cells that are very nearly normal, and 5 represents cells that don't look or act much like normal prostate cells at all. The Gleason score, or sum of the two most common Gleason grades (and therefore on a scale from 2 to 10), tends to predict the aggressiveness of the disease and how it will behave in your body. Tumors with higher Gleason scores, typically above 7, tend to be more aggressive.
2. The PSA level that you had before you were diagnosed with prostate cancer, known as your pre-diagnostic PSA, is often used as an indicator of how advanced your cancer was before it was detected. Usually, the higher the PSA, the more aggressive the disease.
3. Nomograms are simplified charts that have been specially constructed to weigh different contributing factors and to provide a single assessment of the likelihood of remaining disease-free after treatment. They can play an important role in helping to decide whether to undergo additional treatments or whether to enroll in clinical trials assessing new therapeutic regimens or agents.
4. Active surveillance might be appropriate for men who, for one reason or another, have decided not to undergo immediate surgery or radiation therapy. For example, immediate treatment might not make sense for men who have very slow growing or very early cancers, while men who have other serious medical conditions might not be healthy enough to undergo surgery or radiation therapy.
5. During prostatectomy, the prostate and nearby seminal vesicles are removed. If performed *laparoscopically*, a few small incisions are made and blood loss is typically minimized. However, the procedure is technically difficult and the learning curve is steep. Surgical skill with this approach is key.
6. The decision on whether to *attempt* a nerve-sparing procedure should be yours — only you can know how important it is to maintain your erectile function. But ultimately the decision on whether to *perform* the nerve-sparing procedure is up to the surgeon based on his or her years of experience and expert clinical judgment. If the surgeon does not feel that he or she can cure your cancer and leave the nerves intact, the nerves will not be spared.
7. The goal of radiation therapy is to kill the prostate cancer cells where they live. To accomplish this, very high doses of x-rays are delivered to the prostate, concentrated on the small clusters of tumor cells that comprise the cancer within the prostate gland.
8. The most common type of radiation therapy is *external beam radiotherapy*. Radiation oncologists and technicians use CT scans and MRIs to map out the location of the tumor cells, and x-rays are targeted to those areas. With *brachytherapy*, tiny metal pellets containing radioactive iodine or palladium are inserted into the prostate. Over the course of several months, the seeds give off radiation to the immediate surrounding area, killing the prostate cancer cells.

What to Consider When You've Been Diagnosed With Early-Stage Prostate Cancer

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9. A number of studies have shown that the use of *neoadjuvant hormone therapy* can shrink larger tumors, thereby making it easier for oncologists to localize the radiation needed to kill the tumor cells, and significantly improving outcomes. This approach is now used in many institutions for men with high-grade or bulky cancers.
10. The three most significant clinical factors used to determine which initial therapy might be best are the extent of your tumor, your overall health, and your age. Psychological factors can also play an important role: only you can know how you want to deal with your disease and whether the potential side effects of one treatment outweigh those of another.
11. Technique plays an important role in determining whether urinary control and function will be maintained after surgery, and sparing the urinary sphincter is key. But pre-surgical urinary function can play an important role as well. If you've already experienced some hesitation and/or lack of bladder control, it will be harder for you to regain full control and function.
12. During prostatectomy, damage to the rectum is rare, and the bowel changes seen in the first few weeks following surgery are more likely the result of the body adjusting to the increased abdominal space with the loss of the prostate. Radiation therapy, however, can cause significant damage to the rectum, resulting in diarrhea or frequent stools; fecal incontinence or the inability to control bowel movements; and/or rectal bleeding. Much depends on practitioner skill, so be sure to select a doctor who possesses the experience and skill to spare the rectal tissue as much as possible.
13. Regardless of whether the nerves were spared during surgery or whether the most precise dose planning was used during radiation therapy, nearly all men will experience some erectile dysfunction for the first few months after treatment. However, within one year after treatment, nearly all men with intact nerves will see a substantial improvement.
14. Despite the best efforts of surgeons and radiation oncologists, it is nearly impossible for a man to retain his ability to father children through sexual intercourse after undergoing localized treatment for prostate cancer. For men who wish to father children after surgery or radiation therapy, the best chance for fertility is sperm banking; after thawing the frozen semen, up to 50% of sperm will regenerate and can be used for artificial insemination.
15. Dietary and lifestyle changes should be an important part of every man's battle with prostate cancer, complementing any drug therapy, surgery, and/or radiation treatment that you might undergo. Eating healthier foods and exercising more will help keep your body strong to help fight off your disease.

What to Consider When Your PSA Starts to Rise After Initial Treatment

1. In the post-prostatectomy setting, the most widely accepted definition of a recurrence is a PSA > 0.3 ng/mL that has risen on at least two separate occasions at least two weeks apart and measured by the same lab. In the post-radiation therapy setting, the most widely accepted definition is a PSA that has risen from nadir in at least three consecutive tests conducted at least two weeks apart and measured by the same lab. It's important to always use the same lab for all of your PSA tests because PSA values can fluctuate somewhat from lab to lab.
2. *PSA velocity* or *PSA doubling time*, both of which measure the rate at which your PSA rises, can be a very significant factor in determining is the aggressiveness of your cancer. Men with a shorter PSA doubling time or a more rapid PSA velocity after initial therapy tend to have more aggressive disease, and are therefore more likely to need more aggressive therapies.
3. If your PSA starts to rise after you've undergone prostatectomy, "salvage" radiation therapy might be a good option to explore. With this approach, external beam radiation is delivered to the area immediately surrounding where the prostate was, in the hopes of eradicating any remaining prostate cells that have been left behind.
4. With 3-D conformal radiotherapy, IMRT, and brachytherapy, local tissue damage is often kept at a minimum, and surgeons at some of the larger cancer centers have been seeing improved results with "salvage" prostatectomy. But even under the best of circumstances, post-radiation surgery is a very difficult operation to perform, and few surgeons across the country perform it regularly.
5. Regular monitoring of PSA levels after primary therapy is key, as is prompt initiation of treatment upon disease recurrence. The earlier the treatment is begun, the better the likelihood of improved results.
6. Androgen deprivation therapy ("hormone therapy") is a key treatment strategy for prostate cancer that has recurred following local treatment. The goal of all hormone therapies is to stop the production and/or interfere with the effects of testosterone which fuels the growth of prostate cancer cells. However, because not all prostate cancer cells are sensitive to increases or decreases in testosterone levels, hormone therapy is a treatment for prostate cancer but does not cure the disease.
7. There are several approaches to blocking the *secretion* of testosterone including the surgical removal of the testes, drugs known as LHRH agonists, and estrogens.
8. Antiandrogens block the *action* of testosterone by preventing the active form of testosterone known as DHT from entering the central part of the prostate cancer cell; without DHT, the growth of prostate cancer cells is halted.

What to Consider When Your PSA Starts to Rise After Initial Treatment

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9. Testosterone is the primary male hormone, playing an important role in establishing and maintaining the typical male characteristics, such as body hair growth, muscle mass, sexual desire, and erectile function. Most men who are on hormone therapy experience at least some of the effects related to the loss of testosterone, but the degree to which you will be affected by any one drug regimen is impossible to predict.
10. LHRH agonists, the most commonly used drug class for hormone therapy, are given in the form of regular shots: once a month, once every three months, once every four months, or once per year. These long-acting drugs are injected under the skin and release the drug slowly over time.
11. Antiandrogens can be helpful in preventing the “flare” reaction associated with LHRH agonists resulting from an initial transient rise in testosterone. Their use for at least the first 4 weeks of LHRH therapy can relieve the symptoms often seen from the flare reaction, ranging from bone pain to urinary frequency or difficulty.
12. With *intermittent hormone therapy*, the LHRH agonist is used for six to twelve months, during which time a low PSA level is maintained. The drug is stopped until the PSA rises to a predetermined level, at which point the drug is restarted. During the “drug holidays” in between cycles, sexual function and other important quality of life measures might return. However, the clinical benefits of this approach remain unclear, and large clinical trials are currently underway to evaluate its use in this setting.
13. Deferring hormone therapy until metastatic disease can be detected might be an appropriate option for some men. In such cases, the goal would be to reserve an effective, albeit temporary, treatment option until it’s clearly needed.
14. Hormone therapy typically is effective for only a few years. For many men who were using an antiandrogen in combination with an LHRH agonist, stopping the antiandrogen, or *antiandrogen withdrawal*, is the most common first step in secondary hormone therapy. Switching to a different antiandrogen might also be able to offer an extra few months of benefit, and drugs known as *ketoconazole* or *aminoglutethimide* can be used to block the small amounts of testosterone produced by the adrenal glands from being released.
15. Carefully review the side effect profile of the different hormone therapy regimens, and discuss with your health care team potential ways to minimize the effects. In the end, it’s important that you not only understand the value of the therapy in the management of your prostate cancer, but also that you learn how to live your life as best as possible while fighting the disease.

What to Consider When Your PSA Starts to Rise During Hormone Therapy

1. A rising PSA during hormone therapy doesn't mean you're out of options — it means you need to consider the use of other systemic therapies such as chemotherapy or agents that target prostate cancer bone metastases.
2. The primary goal of chemotherapy is to stop the cancer cells from dividing and the cancer cells from growing. But when we look at whether a drug is working, there are generally two levels of effectiveness — whether a drug is palliative, meaning whether it can alleviate symptoms, and whether it can affect the cancer cell growth significantly enough to prolong life.
3. The benefits of chemotherapy in prostate cancer were only first realized recently: mitoxantrone (Novantrone) was approved by the FDA in 1996 when it was shown to provide palliative benefit to men with advanced prostate cancer; docetaxel (Taxotere) was approved in 2004 when it was shown to prolong the lives of the men who took it and relieved symptoms better than mitoxantrone.
4. Although all chemotherapy drugs are designed to slow or stop the growth of cancer cells, each one tends to work in a slightly different way, and using two or more together or one after another in a row can often be more effective than just using one drug alone.
5. Pay close attention to *your* reactions to the different chemotherapy drugs. You're the only one who really knows your own body, so you're the only one who can know whether you are able to tolerate a particular treatment regimen.
6. Don't be too tough or "macho." There are plenty of drugs available to help ward off or treat the different side effects of chemotherapy.
7. Focus on yourself. It doesn't matter what you do, as long as it can help you relieve stress and can help you with the most important part of your cancer treatment — getting well.
8. Prostate cancer cells that have spread beyond the prostate seem to prefer bone tissue and tend to migrate there after escaping the pelvic region. Once the cells settle in, they're known as *prostate cancer bone metastases*. Unlike bone cancer, which originates in the bone, prostate cancer bone metastases are actually collections of prostate cancer cells that happen to be sitting within the bones.
9. When prostate cancer cells settle in the bones, they interact with the bone cells, causing new bone cells to grow and causing the bone tissue to break down. The dye-like material that's injected during a bone scan highlights areas of bone metabolism or activity — areas where bone tissue is changing more rapidly than it normally would in a healthy adult male.

What to Consider When Your PSA Starts to Rise During Hormone Therapy

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10. Men who experience pain from a bone metastasis will often be treated with radiation targeted directly to the metastasis or with radiation-emitting drugs that settle in the metastasis after being injected through a vein. The radiation will kill the prostate cancer cells in the metastasis and thereby relieve the pain.
11. Bisphosphonates are drugs that are designed to help reset the balance in the bone between bone growth and bone destruction which is disrupted by the prostate cancer bone metastases. Zoledronic acid (Zometa) is a bisphosphonate given intravenously that can delay the onset of complications associated with prostate cancer bone metastases and relieve pain. It is typically given once every three weeks as a 15-minute infusion.
12. As the bones in the spine weaken, they can collapse one of top of the other, compressing the spinal cord and the nerves that run out from it. Cord compression associated with metastatic prostate cancer can cause serious problems if not managed immediately, so be sure to tell your doctors about any new pain, weakness, or changes in bowel habits, any of which can result from spinal cord compression.
13. Cancer can be painful, and there's no benefit in acting stoic and pretending it doesn't affect you. There are plenty of very effective pain medications available, and using them will allow you to feel better and stay stronger.
14. Don't assume that you can't get pain relief unless you're completely doped up. Some very simple and easy to take oral medications might be enough to ease your pain.
15. Don't worry about becoming addicted to pain medication. Taking pain medications so that you can spend your days feeling healthier and stronger is the opposite of addictive behavior. However, both physical dependence and tolerance are possible as your body starts to get used to the drugs, so you and your doctors should take them into consideration as you start and stop different pain medications.
16. Consider enrolling in a clinical trial of an experimental new treatment or regimen. Clinical trials are the only way that new and better treatments will be developed and tested appropriately.



Questions to Ask Your Doctor

When You've Been Diagnosed With Early-Stage Prostate Cancer

- What is my “Gleason score” and what does this mean in terms of our approach to my treatment and my prognosis?
 - What is my PSA level? Have we collected multiple PSA values over time so that we can determine if my PSA level is rising? If so, how rapidly is it rising?
- Based upon what we know today, has my cancer spread beyond the prostate? What is the cure rate for this type of cancer?
 - Are there additional tests that we can do to gain the most complete understanding of the stage and aggressiveness of my cancer?
 - What are all of the treatment options for this stage of cancer?
 - What are the benefits of the type of therapy you are recommending?
 - What are the drawbacks/side effects of this type of therapy?
 - Will I have problems with incontinence or impotence?
- Will I have other urinary or rectal problems?
 - What other treatment(s) might be appropriate and why?
 - Are you comfortable with me exploring other treatment options and speaking with other specialists before deciding upon a final plan of action?
 - Is my cancer likely to come back based on what you know today?
 - What can I do to improve the success of my therapy?
 - What kind of follow-up can I expect after treatment?
 - Are there dietary changes that I could or should make to optimize my treatment?
 - Should I join a clinical trial?

Questions to Ask Your Doctor
When You've Been Diagnosed With
Early-Stage Prostate Cancer



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Obtaining answers to these questions, and possibly many more that you can think of, is an important step in learning as much as you can about prostate cancer. Knowing the advantages and disadvantages of the different treatment approaches can help you feel better prepared to deal with your prostate cancer — and help you work with all members of your health care team to find the treatment path that's right for you.



Prostate
Cancer
Foundation

Questions to Ask Your Doctor When You've Been Diagnosed With Early-Stage Prostate Cancer

— If You're Considering Undergoing Surgery —

- Which surgical technique will be used?
 - Based on your experience, why is this the right approach for me?
-
- Do you plan to employ a nerve-sparing technique with the aim of conserving my ability to get an erection following surgery?
 - What level of success have you had in preserving potency (ability to get an erection) in your patients following surgery?
 - What about preserving urinary continence (bladder control)?
 - What will you do if you find cancer outside of my prostate during the surgery?
 - Will that change my prognosis and future treatment?
-
- Do I need to be concerned about blood loss during the surgery? Should I store my blood or get my family and friends to donate blood in case it is needed?
 - What can I expect following the surgery in terms of recovery time? How long will it be before I can return to my normal activities?
 - What are the likely or possible side effects of the surgery, both short-term and long-term?
 - What will we do to monitor my prostate cancer following the surgery?

Obtaining answers to these questions, and possibly many more that you can think of, is an important step in learning as much as you can about prostate cancer. Knowing the advantages and disadvantages of the different treatment approaches can help you feel better prepared to deal with your prostate cancer — and help you work with all members of your health care team to find the treatment path that's right for you.



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Questions to Ask Your Doctor
When You've Been Diagnosed With
Early-Stage Prostate Cancer



— If You're Considering Undergoing Surgery —



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Questions to Ask Your Doctor When You've Been Diagnosed With Early-Stage Prostate Cancer

— If You're Considering Undergoing Radiation Therapy —

- Which radiation technique will be used?
 - Based on your experience, why is this the right approach for me?
- How will this procedure precisely target the cancer tissue but leave the normal tissue unharmed?
 - Are there specific radiation therapy approaches that we should discuss or consider, such as IMRT or brachytherapy?
 - What dose of radiation will you be using and how/why did you select that dose of radiation?
 - How often will I need to come into the clinic for treatments?
 - Do you recommend that we initiate androgen deprivation therapy (“hormone therapy”) before the radiation treatments? Why or why not?
- What level of success have you had in preserving potency (ability to get an erection) in your patients following this type of radiation therapy?
 - What about preserving urinary and bowel continence (bladder and bowel control)? Are there other urinary or bowel side effects that I should be concerned about?
 - What can I expect following the treatments in terms of recovery time? How long will it be before I can return to my normal activities?
 - Are there delayed side effects that might appear over time?
 - What will we do to monitor my prostate cancer following the radiation?

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— If You're Considering
Undergoing Radiation Therapy —



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Questions to Ask Your Doctor

When Your PSA Starts to Rise After Initial Treatment

- What does it mean that my PSA level is rising again?
 - What is my PSA level now and how will we monitor changes over time?
 - Can we (should we) chart the velocity or doubling time of my PSA? What can this tell us about my prognosis?
- Am I a candidate for local “salvage” prostatectomy or radiation? Why or why not?
 - Should I get a bone scan to see if the cancer has spread to my bones?
 - If you recommend that I initiate androgen deprivation therapy (“hormone therapy”), how will this benefit me and slow down the growth of the cancer cells? Is this the optimal time to initiate this treatment?
 - What are the benefits and drawbacks/side effects of hormone therapy? Are there things that I can do to minimize the side effects?
 - If I initiate hormone therapy, will this make my PSA drop back to zero? Will we monitor my PSA over time to see if it’s working?
- How long do the treatment effects of hormone therapy last?
 - If the hormone therapy stops working, what treatment options remain?
 - Are there dietary changes that I could or should make to optimize my treatment?
 - Should we add a medical oncologist to my treatment team to gain an additional perspective on treating my disease?
 - Should I consider joining a clinical trial?

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When Your PSA Starts to Rise After
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Questions to Ask Your Doctor

When Your PSA Starts to Rise During Hormone Therapy

- Since my PSA is rising again, do we discontinue the androgen deprivation therapy (“hormone therapy”)? Why or why not?
 - Are there additional hormone therapy approaches that we should explore?
 - Should I get a bone scan to determine if the cancer has spread to my bones? What will the bone scan tell us?
- Are there therapies that might help slow down the disease progression, especially to prevent the spread of the cancer to my bones?
 - If there is evidence that the cancer has spread to my bones, how can we treat it, slow down the progression and/or prevent bone pain?
 - What are all of the treatment options available to me at this time?
 - Is it important to consider the sequencing of treatment options so that we preserve as many options as possible in the future? Are you recommending any treatments that might prevent me from qualifying for a clinical trial in the future?
- Should we consider chemotherapy?
 - What other treatment(s) might be appropriate and why?
 - What are the side effects of the treatment plan that we have selected?
 - Are there dietary changes that I could or should make to optimize my treatment?
 - Are there any other specialists that we should or could add to my treatment team to gain an additional perspective on treating my disease?
 - Should I consider joining a clinical trial?

Questions to Ask Your Doctor
When Your PSA Starts to Rise During
Hormone Therapy



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