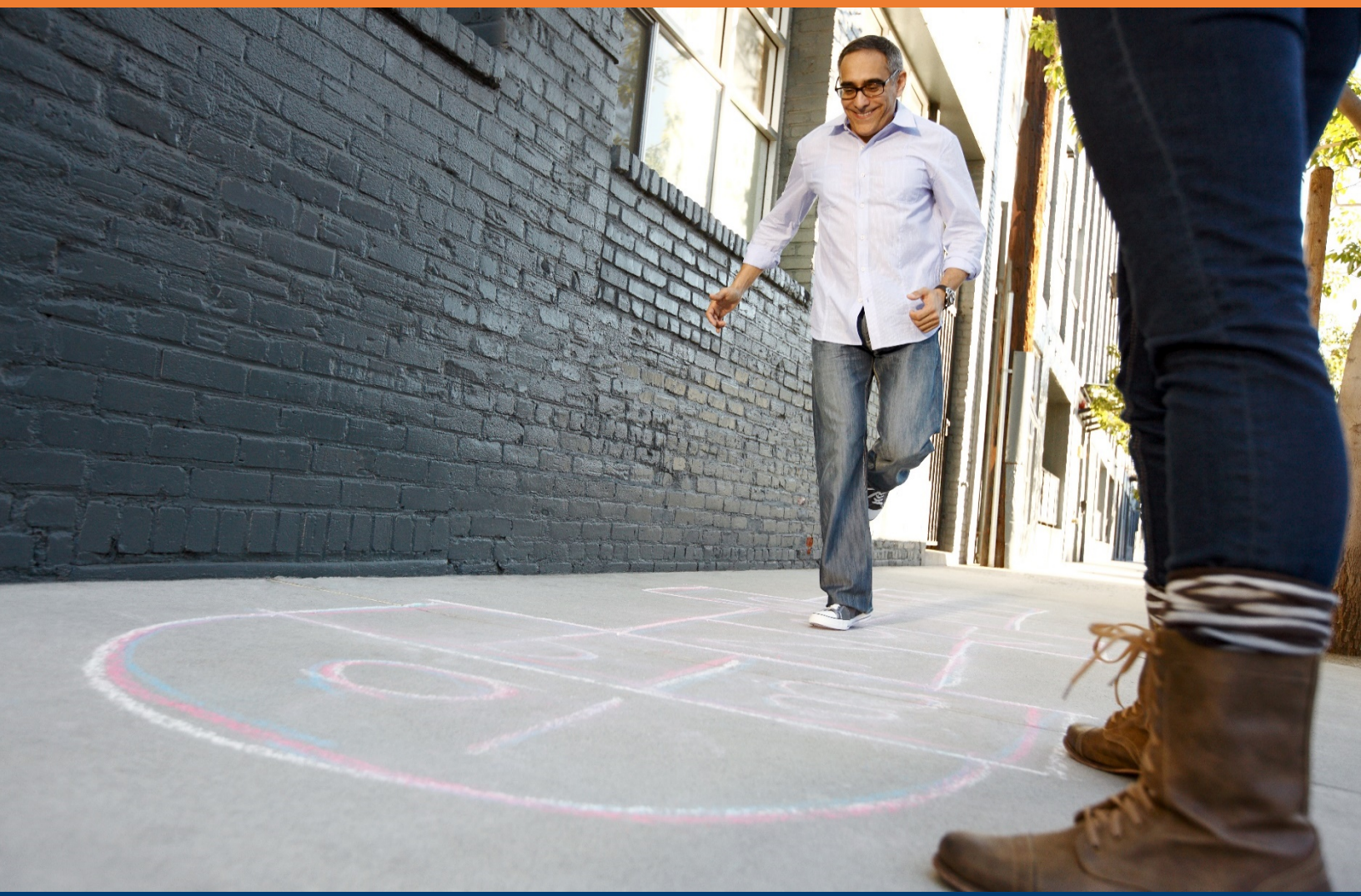
Prostate Cancer ACTION PLAN

Choosing the treatment that's right for you



This guidebook will help you talk with your doctor and make an informed decision together about the treatment that's right for you.

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Prostate Cancer ACTION PLAN, 2nd Edition

Endorsed by Kaiser Permanente Inter-regional Chiefs of Urology

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2nd Edition, © 2020, revised upon special commission of The Permanente Federation, LLC, by: Stephen Lieberman, M.D., John Lam, M.D., MBA, FACS, Stephen G. Williams, M.D., Alex Chen and Joseph Presti, M.D., FACS

Disclaimer

This guidebook provides general recommendations for patients with prostate cancer. Prostate cancer is a complex disease, with different treatment recommendations for individual patients. This guidebook will help you talk with your doctor and make an informed decision together about the treatment that's right for you.

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Introduction

Being diagnosed with prostate cancer is a life-changing event. 12%, or 1 out of 9 men in the United States, will be diagnosed with prostate cancer during their lifetimes (***SEER****** data). Each year, there are around 175,000 new cases of prostate cancer, and an estimated 32,000 men will die from this disease.[1] It is a common disease. For the most part, prostate cancer is relatively slow growing, which means that it can take years to become big enough to be detectable, and even longer to go outside the prostate, or metastasize.

There are over **2.6 million men** in the United States who either have prostate cancer, or have been cured of prostate cancer.

This guidebook was developed to help you talk with your doctors about treatment options. The goal of this conversation is to make an informed decision together about the most appropriate treatment for you.

What's important to understand is that there are many different types of prostate cancer and when it comes to treatment: "one size does not fit all." In addition, significant personal and lifestyle preferences will affect your decision. We are here to help you work through this complex decision.

If your cancer is diagnosed early while still confined to your prostate, you have an excellent chance of being cured.

What you need to know about your diagnosis is that there is generally more good news than bad, and that each prostate cancer is unique. More than 90% of all prostate cancers are detected when the cancer is still in the prostate or the area around it, so success rates of treatment are generally high compared to most other types of cancer. The good news is that if you are diagnosed early while the disease is still confined to the prostate, you have an excellent chance of being cured. However, it is important to keep in mind that prostate cancer is still a deadly disease for some men as it is the second leading cause of cancer-related deaths among American men. Since each cancer is unique, an optimal treatment decision for you may be totally different for the next patient. Your urologist's main goal is to manage the cancer with as few side effects as possible. However, not all prostate cancers need to be treated, as some may never cause any harm to patients for the duration of their lives.

So, the first decision to be made is whether to treat your cancer. "No treatment" is not the same as ignoring the cancer. If your unique cancer is one that falls into the realm of those cancers "unlikely to do harm," you may be a candidate for what is called ***active***

surveillance. In fact, 25%-30% of men with newly-diagnosed prostate cancer may be candidates to safely undergo active surveillance, in which they are monitored without immediate treatment, including treatment-related side-effects, while preserving their chances of long-term survival if the cancer becomes aggressive enough in the future to require treatment.[2-4]

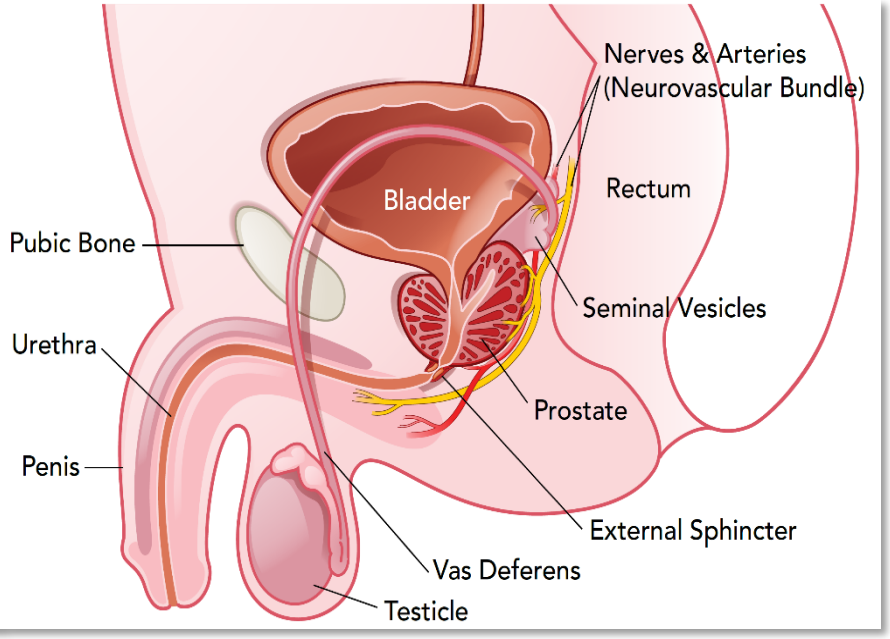
We discuss active surveillance in detail in this guidebook. To understand the complexity of choosing the best treatment option, let's start with a discussion of prostate anatomy, followed by a discussion of what we mean by "cancer grading" and "cancer staging."

Know Your Prostate

It is important to understand prostate anatomy when we start talking about various treatment options and the potential risks and side effects from these treatments.

The prostate is a gland that sits behind or underneath the pubic bone. It's located between the bladder, which stores and then expels urine, and the urethra, which is like a tube or a conduit for both urine and semen. The prostate is like an orange with the bladder on one side and the urethra on the other. The ***urethra***, which is like a drinking straw, goes right through the center of the orange, and then continues to the tip of the penis. The prostate is only present in men. It is important for reproduction because it supplies the fluids needed for sperm to survive and it helps to push the semen out during ejaculation.

It is important to understand prostate anatomy when we start talking about various treatment options and the potential risks and side effects from these treatments.



The prostate is divided into several different anatomical regions, or zones.[5] The majority of prostate cancers arise from the peripheral zone (outer portion of the prostate) next to the rectum, which is the lower end of the intestines that connects to the anus. That is why a doctor's examination of the prostate with a gloved finger in the rectum, known as a digital rectal exam (DRE), may be helpful in detecting some prostate cancers.

On the penis side of the prostate, there is a valve that opens when men urinate (active voiding) and closes when the bladder is filling with urine (storage phase). This important valve is called the external ***sphincter***. The tube that goes through the valve is called the

membranous urethra. Where the bladder is attached to the prostate there is another mechanism made up of smooth muscle called the internal sphincter. This valve is affected by drugs called alpha blockers, commonly known as tamsulosin (Flomax®), doxazosin (Cardura®), terazosin (Hytrin®), alfluzosin (Uroxatral®), and silodosin (Rapaflo®).[6] These drugs relax the internal sphincter and allow it to open better, thus improving the stream and promoting better bladder emptying.

Sperm leaves the testicles and travels through the vas deferens to the prostate. Before entering the prostate, the vas deferens joins a tube called the ejaculatory duct, which also receives tubes from the seminal vesicles, two glands that sit behind the bladder on top of the prostate and store fluid that nourish the sperm. The ejaculatory ducts go through the prostate and empty into the urethra, which carries both urine and semen out of the body. During ejaculation, the internal sphincter closes, which forces the semen out through the penis.

You can clearly see how the location of your prostate can complicate treatment and possible side effects such as impotence or incontinence.

Finally, there are two sets of nerves and blood vessels (arteries and veins), called the **neurovascular bundles**, that are adjacent to and run along each side of the prostate to enter into the penis helping to drive erections.[7] The neurovascular bundles travel from the lower spinal cord through the pelvis to the penis. Since the neurovascular bundles are close the prostate, they can often be disturbed during treatment for prostate cancer. They can also be directly invaded by more aggressive cancers.

Biology of Prostate Cancer

It is important to understand how prostate cancer grows in order to properly understand the diagnosis and treatment options. Androgens, such as testosterone and dihydrotestosterone, are hormones that are important for many male characteristics and aspects of reproduction. They are processed by the prostate as part of its normal everyday function. Testosterone is primarily made in the testes, but a smaller amount is made in the adrenal glands above the kidneys.

When prostate cancer forms, the cancer feeds on these same androgens and uses them as fuel for growth. Therefore, one of treatments for men, especially those with

advanced prostate cancer, is to lower androgen levels with drugs termed “hormone therapy” or androgen deprivation therapy (ADT).[8]

Sometimes cancer cells will escape the prostate spreading to nearby tissue. Lymph nodes are often the first destination, and if this is the case, it means that there is a higher chance that it has spread to other parts of the body as well. If prostate cancer cells gain access to the bloodstream, they can be deposited in various sites throughout the body. Bones are the most common site (85% to 90% metastatic cases) as well as other organs such as the liver or lungs.[9-10]

Prostate-Specific Antigen (PSA)

Prostate-Specific Antigen (PSA) is a protein produced by the prostate and is found mostly in the semen, with very small amounts released into the bloodstream.[11] It is used as a prostate cancer marker because more PSA is released when there is development and growth of prostate cancer.

PSA is not a perfect test to screen for prostate cancer because elevated levels can be caused by benign prostatic hyperplasia (enlarged prostate) or prostatitis (infection or inflammation of prostate). In fact, there is active debate surrounding prostate cancer screening. There are some healthcare professionals who are concerned that increased PSA screening finds tumors that grow so slow not to pose any long-term threat and may lead to “overtreatment” to men with low-risk cancers leading to unnecessary side effects and impacting quality of life. However, there is significant data to suggest that PSA testing has decreased prostate cancer death rates because men with aggressive cancers are being diagnosed and treated earlier.

There is a small proportion of men who may consider prostate cancer screening at an earlier age due to an increased risk of prostate cancer because they may be carrying an inherited cancer risk gene or have strong family history of cancer. It is important to understand that there is no “normal” PSA level. Rather we know that the higher the PSA level, the higher the risk of prostate cancer. It is also important to recognize that, in the absence of cancer, PSA increases with age and screening PSA levels are often compared to normal values for the man’s age group.

It is also worth noting that in rare cases (<2%), men who have a low PSA have clinically significant prostate cancer.[12] Unfortunately, in most of these cases, disease does not present until it has progressed beyond the prostate and become symptomatic.

Current guidelines for prostate cancer consider life expectancy to be an important factor when making screening and treatment decisions. For patients with life expectancy <10 years, prostate cancer screening and active surveillance or definitive treatment of low-risk disease is not recommended. Information on life expectancy may encourage conversations about goals of care, and ultimately lead to improved shared decision-making. Life expectancy estimates may prove useful when counselling on the long-term risks and benefits of screening or treatment in the context of patients' existing comorbidities.

Three Things to Know in Choosing Your Treatment

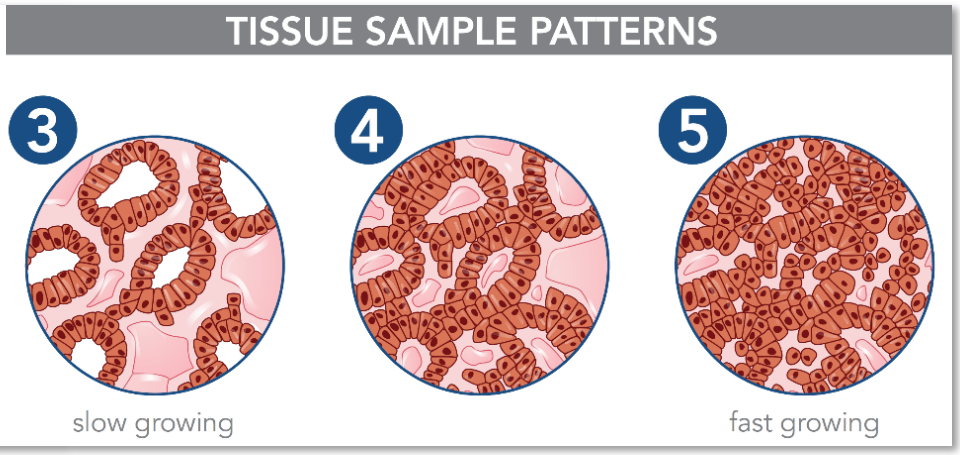
1. Cancer Grade

When we talk about ***cancer grade***, we're referring to what the cancer looks like under the microscope. Prostate cancer is an abnormal growth of some of the glands of the prostate. We look at the pattern or architecture, of the glands as well as the appearance of each individual cell. The system used worldwide to describe prostate cancer is the Gleason Scoring System, named for Dr. Donald Gleason, the pathologist who originally developed it in 1966.[13]

To determine a ***Gleason score*** we generally take at least 12 tissue samples, or biopsies of the prostate. These samples are about 1-1.5 cm long and 0.2 cm in diameter. Each sample may contain varying amounts of cancer. For instance, in one core sample, normal tissue can be replaced by a small amount (say 5%) of cancer, while in another core, the entire core (100%) can be cancer. The pathologist assigns a number to each area of the cancer based on the appearance and arrangement of the glands – this is the ***Gleason grade***.

In the past, pathologists assigned a grade from 1-to-5 to the cancerous tissue in each biopsy based on architecture and microscopic appearance using a 4x-10x objective eyepiece shown to predict outcome in prostate cancer. However, Gleason grades 1 and 2 are no longer recommended for use since these patterns have an outcome no different than grade 3, so cancers are now graded on a scale from 3-to-5.

The Gleason Scoring System is used worldwide to describe what prostate cancer looks like under a microscope.

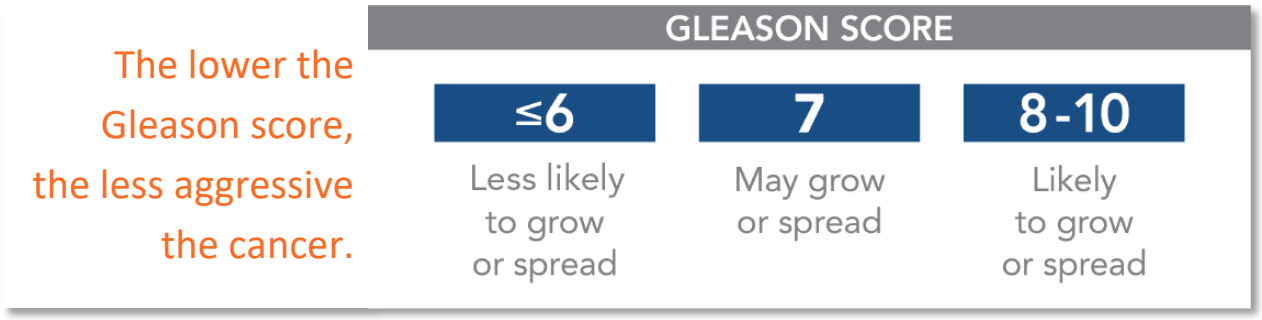


Three is a slow-growing cancer and 5 is a fast-growing cancer. Each tissue sample can be all the same Gleason grade – such as all 3s – or it can be a mixture of Gleason grades – such as some 3s and some 4s.

To determine the Gleason score, the pathologist adds the most prevalent Gleason grade, and the second most prevalent Gleason grade. For example, a man with Gleason grades of 3 in all his samples has a Gleason score of 6 (3+3). A man with Gleason grades of 4 and 5 has a Gleason score of 9 (4+5).

The Gleason score is a major factor that differentiates one cancer from another. So even though 10 men may share a diagnosis of prostate cancer, chances are, their cancers are not all the same. Some men may have cancer with Gleason scores of 6 or 7; others may have cancer with Gleason scores of 8, 9, or 10. That's why we say that all prostate cancers are not the same and why treatments may differ from man to man.

Generally speaking, Gleason score cancers of less than 6 are no longer reported. We commonly find Gleason 6 and 7 cancers. Gleason 8, 9, and 10 cancers are less common. Cancers with lower Gleason scores are less aggressive, grow slowly, and are less likely to spread. The opposite is true for higher Gleason scores. These tumors are aggressive, grow fast, and spread.



Grade Group

In 2014, the International Society of Urological Pathologists (ISUP) released a revised prostate cancer grading system, called the Grade Groups, which simplifies the system with just five grade groups, 1 through 5.[14]

Risk Group	Grade Group	Gleason Score
Low	Grade Group 1	Gleason Score ≤6
Intermediate Favorable	Grade Group 2	Gleason Score 7 (3+4)
Intermediate Unfavorable	Grade Group 3	Gleason Score 7 (4+3)
High	Grade Group 4	Gleason Score 8
Very High	Grade Group 5	Gleason Score 9-10

Risk Categories

Another way of looking at the Gleason Scoring System is that Gleason 6 tumors are "low risk," Gleason 7 are "intermediate risk," and 8-10 are "high risk." The problem is that "risk" is often poorly defined. The risk with prostate cancer is that it may grow rapidly and spread locally outside of the prostate. Or there is a risk that it will spread to other organs, specifically, but not limited to, bones and ***lymph nodes***. In talking about risk, there is a correlation with treatment failure, which means the higher the risk, the more likely the treatment will fail. Lastly, there is the risk of death.

We will discuss risk categories later. There is more that goes into determining risk than Gleason score alone.

2. PSA Level

Knowing your PSA level can also give you more good information about your cancer. Prostate-specific antigen – or PSA – is a protein produced exclusively by prostate cells. Men with prostate cancer often have higher PSA levels in their blood.

Prostate-specific antigen, or PSA is a protein produced exclusively by prostate cells.

Interpreting PSA levels is complicated. PSA levels can vary widely based on how these levels correlate with:

- Aggressiveness
- Existing ***metastases***
- Potential for spread

Your doctor will help you understand your PSA levels. There are many factors that go into how the PSA levels are used in explaining treatment options.

3. Tumor Stage

The third important factor in determining risk is the "tumor stage." Tumor staging can be complicated because there are so many variables including:

- Size of the tumor
- If it can be felt on digital rectal exam or seen on imaging tests
- If it is in one or both sides of the prostate
- If it is in the seminal vesicles
- If the ***palpable*** cancer extends to the side walls of the pelvis
- If it has spread to lymph nodes or bones

The staging system is called the "TNM" system:

- T = tumor
- N = lymph nodes (usually prostate cancer spreads first to lymph nodes in the pelvis)
- M = metastases

The T stage ranges from 1 to 4.

Stage T1 cancers are not felt on digital rectal exam or seen on ultrasound. There are 3 subclasses of T1 tumors: a, b, and c. If a man has a transurethral prostatectomy (or "roto rooter" operation) to remove part of his prostate for non-malignant conditions such as prostate enlargement or repeated urinary tract infections and cancer is found in the specimen, then that man has either T1a or T1b staging, depending on how much cancer is detected in the surgical specimens.

- T1a – the number of chips (chips are pieces of the prostate removed during a transurethral prostatectomy) is less than 5% of the total volume of the specimen
- T1b – the number of chips is greater than 5% of the total volume
- T1c – cancer is detected by PSA but cannot be felt on digital rectal exam or seen on imaging

Stage T2 cancers can be felt on digital rectal exam or seen on imaging. There are 3 subclasses of T2 tumors:

- T2a – the cancer is in half or less of one lobe (the prostate has two lobes, right and left)
- T2b – the cancer is in more than one half of one lobe
- T2c – the cancer is in both lobes

Stage T3 disease is when the cancer has begun to grow outside of the prostate and can be felt there or is present in the seminal vesicles. T3a is cancer that extends outside of the prostate on one side or both sides but is not in the seminal vesicles. T3b is cancer that has invaded one or both seminal vesicles.

Stage T4 disease means that the cancer has spread further beyond the prostate and is fixed or invades adjacent structures other than seminal vesicles such as the bladder, ***ureters***, external sphincter, rectum, levator muscles and/or pelvic wall.

There is one more component to highlight. You will sometimes hear about "clinical" and "pathologic" staging. ***Clinical staging*** is based on the rectal exam and core biopsy results. Pathologic staging is based on an examination of the entire prostate after it has been surgically removed. So, you might see a small "c" or "p" in front of the capital "T" to denote this distinction between clinical (c) or pathologic (p) staging.

It's possible that your clinical and pathologic stages might be different. For example, your tumor may be staged cT1 before surgery and pT2 after surgery, meaning that the post-op pathologic examination shows your tumor is larger than indicated by the pre-op clinical exam. Patients who receive radiation or other treatments for prostate cancer in which the prostate is not removed, can only have a ***"clinical" stage***.

Knowing your tumor grade, PSA level, and tumor stage will help you choose a treatment.

"N" or node categories are staged as "N0" if the nodes have been removed and have no tumor in them, "Nx" if they cannot be assessed, or "N1" if the cancer has spread to one or more lymph nodes in the pelvis.

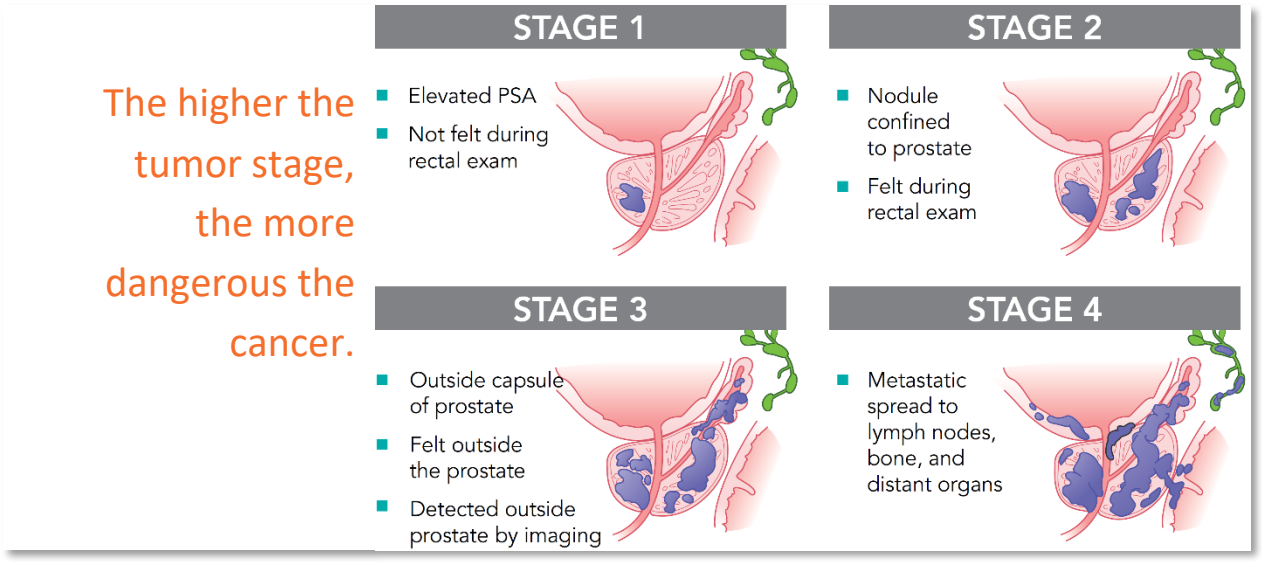
"M" refers to metastases. "M0" means no distant metastases. "M1a" means the cancer has spread beyond the nearby lymph nodes in the pelvis. "M1b" means the cancer has spread to bones. "M1c" means the cancer has spread to sites such as the lung, liver, or brain, with or without bone metastases.

Aggressive cancers (e.g., PSA >20, grade group 4 or 5 [Gleason score 8-10], or stage T3-4) usually warrant imaging scans to determine the presence of metastatic disease.

Some men whose cancer has less aggressive features may benefit from further imaging and they should discuss this with their doctor. This is most commonly done with a computed tomography (CT) scan or an MRI and a bone scan, although newer and more sensitive imaging technologies are in development, such as molecular PET imaging (e.g., PSMA, Axumin® (fluciclovine F 18), Choline C-11).

To summarize: the higher the grade and/or the stage, the higher the risk and the more dangerous the cancer. Knowing your tumor grade and stage and your PSA level will help you understand your risk from the specific cancer that's been detected and help you choose a treatment. Understanding the variables that play into risk may explain why your doctor may guide you in one direction rather than another.

In addition to the TNM staging system, sometimes physicians use a Stage Grouping System. This is illustrated below. In general Stages 1 and 2 refer to cancers confined to the prostate, Stage 3 cancers have grown through the capsule, or shell, of the prostate and Stage 4 refers to cancers that have spread or metastasized to distant sites.



Risk Assessment

Your cancer grade, tumor stage, and PSA level are key factors in helping you and your doctor decide about your treatment. It's also helpful to know what we call "risk assessment" and "risk groups."

We all know about risks. Every time we get on the freeway or climb a ladder, we risk having an accident. It's the same with prostate cancer. There's the risk that the cancer will grow, or spread, or even cause death. Or it may not do any of those things. Knowing your risk can help you make a treatment decision.

Knowing your risk can help you make a treatment decision.

Risk groups, as described by the National Comprehensive Cancer Network (NCCN), are categories based on risk of prostate cancer spreading or becoming more advanced using clinical and pathological features such as grade, stage, and PSA.[15] This can help your treatment team decide what additional tests are needed (imaging, germline testing, molecular and biomarker analysis of tumor) and guide initial treatment.

Risk Group	Clinical / Pathologic Features
Very Low	• T1c AND • Grade Group 1 AND • PSA <10 ng/mL AND • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core AND • PSA density <0.15 ng/mL/g
Low	• T1-T2a AND • Grade Group 1 AND • PSA <10 ng/mL
Intermediate	Has no high- or very- high-risk features and has one or more intermediate risk factors (IRF): • T2b-T2c • Grade Group 2 or 3 • PSA 10–20 ng/mL
Favorable	• 1 IRF and • Grade Group 1 or 2 and • <50% biopsy cores positive
Unfavorable	• 2 or 3 IRFs and/or • Grade Group 3 and/or • >50% biopsy cores positive
High	• T3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL
Very High	• T3b-T4 OR • Primary Gleason pattern 5 OR • >4 cores with Grade Group 4 or 5
Regional Nodal	• Any N1, M0
Metastases	• Any M1

Your doctor may also use a nomogram to assess your risk. A nomogram is a mathematical tool used to make predictions. In the case of prostate cancer, nomograms are used to predict the risk that your cancer will spread or recur after treatment. A nomogram is based on detailed information about your cancer including your grade, stage, PSA, and biopsy results. It can predict your individual risk better than assigning you to a risk group.

So, a nomogram can be very useful in helping you and your doctor determine a treatment approach that may give you the greatest benefit.

Your doctor uses various tools to determine the risk that your cancer may or may not spread or recur. Knowing your risk may well help you and your doctor determine the next steps to take in your treatment.

Deciding on Treatment Options

There are a variety of treatment options for prostate cancer. Each therapy has benefits and risks; each has associated 5-year, 10-year, and 15-year survival probabilities both with and without cure. Treatment choice is guided by prostate cancer risk stratification, patient life expectancy, assessment of oncologic and quality of life outcomes, and patient preference.

Options:

1. Active surveillance
2. Surgery
3. Radiation therapy
4. Ablative therapy (destruction of abnormal/cancer tissue)
5. Hormone therapy

There are *different* treatment options for prostate cancer because every man is *different,* and every prostate cancer is *different*.

The treatment you choose may depend on whether or not:

- Your life expectancy is greater than 10 years (based on your comorbidities or other medical problems like heart disease, lung disease, or diabetes)
- You are in the low, intermediate or high-risk group
- Your cancer has a high likelihood of being confined to the prostate (that is, not T3 or T4, no lymph node or bone metastases)

If your cancer meets the above noted criteria, then you would be a candidate for:

- Surgery (radical prostatectomy)
- Radiation (3D Conformal Radiotherapy, Intensity Modulated Radiation Therapy – IMRT, Image Guided Radiation Therapy — IGRT, or Stereotactic Body Radiation Therapy — SBRT) are different forms of EBRT, or External Beam Radiation Therapy
- Brachytherapy (implantation of radioactive seeds)
- Combination Radiation Therapy (External Beam plus seeds)
- Ablative therapy (destruction of abnormal/cancer tissue)

Understanding the variables of your particular cancer may explain why your doctor may guide you in one direction rather than another.

The optimal and most appropriate treatment is based on a variety of factors. We will discuss each therapy at length. Before we do though, it's important to know:

- If the cancer is only in the prostate
- If the cancer is locally advanced (outside the confines or capsule of the prostate or in the seminal vesicles)
- If the cancer is in the lymph nodes, bones, or other organs

When indicated by the PSA level, Gleason score, or clinical stage, a CT scan of the abdomen and pelvis can sometimes detect enlarged lymph nodes. A bone scan will be done to detect spread to bone. Sometimes an MRI scan will be used to detect locally advanced disease.

Assessing Risk

There are also a variety of tools, tables, and ***nomograms*** (a prediction tool) that use the variables of PSA level, Gleason Score, clinical stage, and other variables, to predict the potential for recurrence and/or progression as well as survival.[16]

The optimal and most appropriate treatment is based on a variety of factors.

One online tool used to predict the likelihood that a tumor will or will not spread for patients undergoing radical prostatectomy surgery is the Partin Table, which was developed at Johns Hopkins University.[17] Partin Tables use the variables of Gleason Score, serum PSA, and clinical stage to predict the extent of disease. This is one of the earliest tools developed based on a large historical series of patients treated by a single surgeon. It is important to recognize that even when a cancer is outside of the prostate it can sometimes still be cured with either surgery or radiation. A word of caution, since the Partin Tables were derived from patients treated many years ago, they may over-estimate the chance of more adverse features such as extracapsular extension of lymph node involvement.

Another commonly used online predictive tool are the nomograms, developed at Memorial Sloan Kettering Cancer Center, from a more contemporary series of prostate cancer patients.[18] (https://www.mskcc.org/nomograms/prostate/pre_op)

These tools can include additional information such as how many needles on the biopsy showed cancer which will change these predicted risks. These nomograms provide additional information that may help in choosing a treatment. Ask your doctor if this predictive tool is useful for you.

Let's look at a 65-year-old man who has a:

- PSA of 7
- Gleason Score of 4+3
- Clinical stage T2b

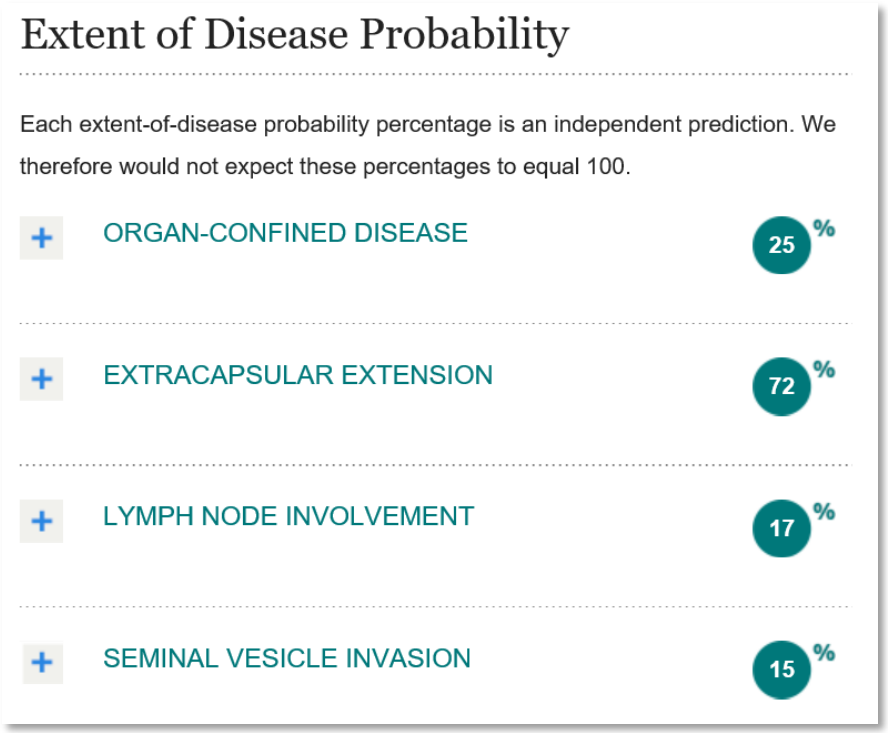
A Partin Table is a tool to predict the likelihood of prostate cancer recurrence or progression.

PARTIN TABLE

Organ Confined (25)	Extracapsular Extension (36)	Seminal Vesicle Involvement (7)	Lymph Node Involvement (5)
24% (19 to 31)	47% (40 to 55)	19% (12 to 25)	10% (5 to 16)

Below are the prediction using the Memorial Sloan Kettering Cancer Center nomogram for the same information:

Memorial Sloan Kettering Cancer Center Nomograms



Notice the two different models provide slightly different risks. It is important to realize these are estimates and it is better to consider broad categories such as “low, medium or high” rather than exact percentages.

Genomic Testing

There are also newer methods of assessing risk on the near horizon**. These are commercially-available “genomic tests” (Prolaris®, ProstaVysion®, Oncotype Dx GPS®, Decipher®) that are based on the actual genes and DNA of the cancer.[19] While early retrospective studies with these tools were encouraging, a large recent prospective study is less convincing and the exact role of these tests in making individual treatment decisions remains uncertain.[20]

So, keep in mind that every patient and every cancer are different. Some cancers can be followed by active surveillance. Other cancers that predictably grow fast and spread can be cured with treatment if detected before local spread or metastases.

When choosing a treatment option, it's important to understand that every treatment has both benefits and risks.

Let’s get back to cancers that are potentially dangerous but probably confined to the prostate – a situation in which the benefit of treatment will likely outweigh the risks. But how do you decide which treatment to have?

Choosing the right option or treatment can be confusing and difficult. Your decision is best made with the help of your doctors. What we are going to talk about next will help you with that discussion.

Active Surveillance

What is active surveillance? Why do it? Who is a candidate? What are the risks and benefits? You may hear 2 terms – ***active surveillance*** and ***watchful waiting***. They are not the same.

Active surveillance is an option for managing your prostate cancer during which you will likely have:

- Periodic PSA tests, usually every 6 months
- Repeat prostate biopsies, usually at intervals of 1 to 3 years
- There are various protocols for active surveillance. PSA testing intervals and the need for repeat biopsy can vary per protocol and clinical situation.

Active surveillance is not the same as “no treatment,” but rather a strategy to follow the cancer closely so that ”treatment” is deferred to only “if and when” it may be needed.

During active surveillance, we look for “triggers” that indicate the cancer is growing or changing and therefore should be treated.

Watchful waiting on the other hand is just as it sounds, it is waiting for the cancer to cause symptoms as a result of progression, enlargement, or spread before use of non-curative or palliative treatments. For all practical purposes, watchful waiting is a practice for patients who don’t need therapy.

Why do active surveillance? Because some prostate cancers are indolent. That means they are of low volume (low stage), low Gleason score, and do not change over time. Men who are elderly and have less than a 15-year life expectancy, or who have multiple

other serious medical problems, are likely not to benefit from treatment of low-volume, low-grade prostate cancer. Even some younger and healthy men who have very low-risk disease may not benefit from invasive treatment and would be needlessly subjected to significant side effects from treatment (impotence, incontinence, voiding difficulties, rectal, bladder or prostate bleeding).

Not all cancers need to be treated.

Who is a candidate for active surveillance? There is no one set protocol for deciding who goes on active surveillance. Generally speaking, a good candidate for active surveillance will have:

- A Gleason Score of 6 or less and in some patients with Gleason score 3+4
- A total PSA of less than 10
- No cancer in more than 2 or 3 out of 12 biopsy cores. Within each positive core, there should be less than 50% cancer.

Some protocols use PSA density (PSA divided by prostate volume which is measured at the time of the biopsy) of less than 0.15 as an inclusion criteria, because it's been shown that the higher the PSA density is above 0.15, the greater the risk of aggressive cancer. Patients with these cancers would potentially be harmed by active surveillance. That is, they have a greater chance of benefiting from definitive treatment such as surgery or radiation.

Some prostate cancers are indolent, which means they are of low stage, low Gleason score, and do not change over time

Benefits of active surveillance include:

- Avoiding the overtreatment of cancers that are indolent and do not need to be treated
- Delaying treatment to avoid the side effects of therapy for as long as possible before definitive therapy is needed
- Eliminating the risks and side effects of definitive treatment

The risk of active surveillance is that not all Gleason 6 low-volume cancers are indolent. In fact, among this group of low-risk patients, there is a 30% risk of "progression".[21] By progression, we mean an increase in tumor grade (Gleason score of more than 6), volume (more than 3 biopsies positive), stage (the development of a palpable cancer on rectal exam), or the low probability of lymph node or bone metastases. This happens either because the initial biopsy missed a more dangerous tumor, or a so-called sampling error occurred (meaning the biopsies missed the tumor), or the cancer changed to a higher, faster growing grade.

The problem is that, at the time of the initial positive biopsy, we can't precisely detect which Gleason 6 low-volume tumors are indolent and which are not. There are currently many scientists looking for genetic markers or molecular signatures that will help us with this problem. Studies are currently ongoing. But keep in mind, that 70% of cancers under active surveillance will not progress in the first five years following diagnosis to require definitive treatment but need to be closely monitored.[2-4]

If you choose active surveillance, what's next? Generally speaking:

- You'll have a PSA test every 6 months.
- If the PSA rises rapidly, it is usually repeated to rule out lab error and if still elevated it will be recommended that you have another biopsy.
- We typically wait 6 months to a year to do the first repeat biopsy.
- If the PSA doubling time is less than 2 years, another biopsy is considered. (Doubling time is the amount of time it takes the PSA to double.)
- There are various protocols for active surveillance. PSA testing intervals and the need for repeat biopsy can vary per protocol and clinical situation. You should discuss with your doctor the specific follow-up protocol you will follow.

Active surveillance may help men delay treatment to avoid the side effects of therapy before definitive therapy is needed.

Depending on your age and other medical problems, treatment is often recommended if there is an increase in Gleason score above 6, or an increase in volume or stage. In some situations, however, treatment may not be recommended even if the cancer appears to have worsened.

You and your urologist need to decide if you are a good candidate for active surveillance and whether you are comfortable with all that is required to decrease the likelihood of missing an opportunity to cure your cancer if needed.

Surgery (Radical Prostatectomy)

For prostate cancer, no matter what surgical method is used to remove the prostate, the operation is called “Radical Prostatectomy.” Surgery to remove the prostate and seminal vesicles can be done a variety of ways. When the operation is done through the abdominal wall and behind the pubic bone, it’s called “Radical Retropubic Prostatectomy.” This is the method used 99% of the time.[22] Another much less common way of doing a radical prostatectomy is via the perineum, which is the space between the scrotum and rectum.

Your surgeon’s experience matters. It’s okay to ask your surgeon how many procedures they have done and their complication rate.

A radical retropubic prostatectomy can be done 3 ways:

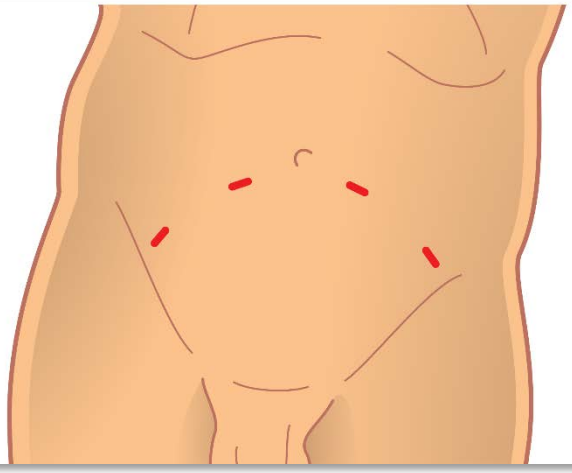
- Robotic-Assisted Laparoscopic
- Pure Laparoscopic (no robot involved)
- Open (via an incision between the belly button and pubic bone)

There are reasons for doing an open prostatectomy or even via the perineum, generally related to your physique and weight, presence of other medical illnesses, and the possibility of lymph node involvement. But close to 90% of modern-day radical prostatectomies in the United States are done robotically using the da Vinci® System, so our discussion will be mainly limited to that procedure.[23] If your urologist is recommending an open radical retropubic prostatectomy, he/she will explain how it differs from a robotic procedure, and the reason for preferring the open procedure.

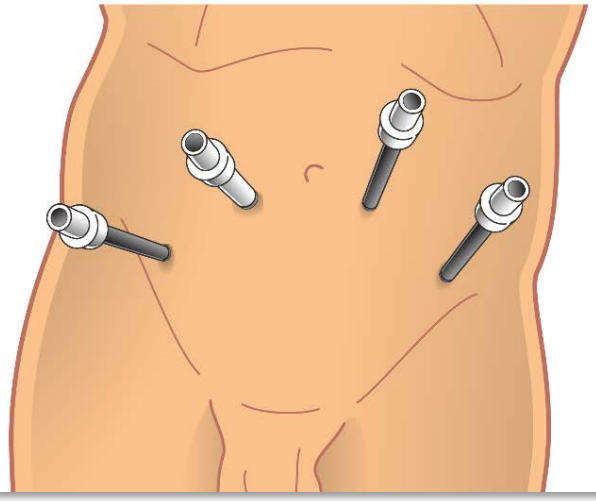
90% of modern-day radical prostatectomies are done laparoscopically using the da Vinci® System.

The robotic prostatectomy procedure is done under general anesthesia. The patient's legs may be in stirrups and the table is tilted so the head is down, and the feet are up. There are two surgeons – one at the bedside, one at the console. Standard laparoscopic access to the abdominal cavity (this being a transperitoneal approach) is obtained and the abdomen is filled (insufflated) with carbon dioxide. Four to six small incisions about ½ inch long are made. Three instruments (two working and one retractor) and a camera are placed through each of the four ports. The instruments and camera are attached to the robotic arms. The camera is very sophisticated and produces a magnified 3D stereoscopic image. The surgeon who sits at the console controls the instruments with his/her hands, fingers, and feet.

Typical placement of the incisions made to perform robotic surgery.



Laparoscopic instruments and a 3D camera are inserted through the incisions to give the surgeon a magnified view and clear access to the prostate.



A pelvic lymph node dissection may or may not be done depending on tumor grade and stage. Veins and arteries are controlled, and the prostate is exposed. It is detached at the bladder neck, and the seminal vesicles are dissected free. If the nerves responsible for potency are spared, they are dissected off the prostatic capsule. Sparing the nerves is done if the tumor volume, grade, and location are favorable for sparing them. We don't want to leave cancer behind, so if the variables present this risk, then the dissection proceeds outside of the neurovascular bundle and this is removed with the specimen. Nerve sparing can be done on one side or both. The urethra is divided a few millimeters from the apex of the prostate and the specimen is placed in a bag and removed.

The bladder then needs to be connected to the urethra at the level of the external sphincter. This is called an ***anastomosis***. The anastomosis is done over a catheter with a running or continuous suture (as opposed to multiple interrupted sutures which is what most surgeons do during an open radical prostatectomy). The surgeon tries to make the anastomosis "watertight" so that urine does not leak at the suture line. Based on your surgeon's preference, a small drain may be placed, and the fluid goes into a small suction bulb. The operation usually takes 2½ - 3½ hours on average and has very little blood loss.

The patient may be discharge home after surgery or stay in the hospital overnight and released to his own home the next day, with the catheter in, where it remains for about a week. If a drain is present, it may be removed, but if there is significant drainage, then he will go home with the drain in. Regular food can be eaten within one day.

The patient is given medication for pain, bladder spasms (symptoms include feeling the need to urinate constantly due to irritation from the catheter), and a stool softener. Risks

and complications are similar to most major complex operations but occur less than 1% of the time.[24-26] Short-term complications may include:

- Major bleeding requiring transfusion
- Infection
- Urine leak
- Bowel or blood vessel injury
- Delayed return of bowel function
- Blood clots in legs and/or lungs

Long-term complications may include:

- Incontinence (urine leak). In large centers where many robotic-assisted radical prostatectomies are done, the risk of incontinence is between 10% and 15%. The risk of severe incontinence is less than 2%.[27] Severe incontinence can be fixed or improved with a second operation such as an artificial sphincter or "urethra suspension" or "sling."

- Impotence (erectile dysfunction or ED). ED can be mild, moderate or more severe and occurs in 40%-60% of patients.[27] Multiple methods of curing or helping ED are available, ranging from drugs like sildenafil (Viagra®), vacuum erection devices, to penile implants.

Both continence and ED are dependent on a patient's age. ED factors that influence post-operative sexual function include:

- Younger patients do better
- Men with better pre-operative sexual function do better
- Whether one, both, or no neurovascular bundles are spared
- Experience and skill of the surgeon

Surgery is not for everybody, but for some patients, surgery is the absolute best option.

Your surgeon will want to maximize return of continence and erectile function and there are things you can do both in the pre- and postoperative periods to help with this. Ask your surgeon what you can do.

How do you know if the surgery cured your cancer? The pathologist examines the entire prostate and seminal vesicles after they've been surgically removed. This exam produces a "pathologic" grade and stage as opposed to the "clinical" grade and stage that were established prior to surgery. The pathologic grade and stage can be worse than or the same as the clinical grade and stage, but it will rarely be better. In other words, the pathologic exam may show that the tumor has a higher Gleason score or more volume than was indicated by the clinical exam.

After surgery, if all the cancer is contained in the prostate, PSA becomes undetectable.

The pathologist looks at the outer margins of the prostate for cancer at the margin, this is called margin-positive disease. The pathologist will also look for cancer around nerves and cancer in blood vessels or lymph channels. Generally speaking, margin positive disease would put you at a higher risk of local recurrence, late recurrence, metastatic disease, and other problem as well as the need for salvage radiation therapy.

However, marginal positive disease does not always progress, and does not always indicate no chance for cure.

Patients with other problematic pathology features at surgery (e.g. extension of cancer beyond the capsule or invasion of the seminal vesicles or lymph nodes) may require additional treatments such as adjuvant radiation and/or hormonal therapy. These decisions are usually made after the first PSA is checked 6 to 12 weeks after surgery.

Additional therapy may also be recommended for men who have cancer found in their lymph nodes at the time of surgery; in this context, hormone therapy after surgery has been shown to help patients live longer.

After surgery, if all of the cancer is contained in the prostate, PSA becomes undetectable. PSA is usually checked every 3-6 months during the first-year post operatively, and then every 6-12 months thereafter. If the PSA is measurable and rising on 2 or 3 consecutive measures, that is considered a ***biochemical or PSA recurrence*** of the cancer. There are several options when this happens, all of which need to be discussed with your urologist, radiation therapist, and oncologist and will not be covered here.

Radiation Therapy

Radiation therapy kills cancer cells by damaging their DNA with ionizing radiation or photons. Radiation can be delivered to the cancer and surrounding tissues externally or by implanting radioactive seeds. External Beam Radiation Therapy (EBRT) can be delivered as 3D conformal radiotherapy, Image Guided Radiation Therapy (IGRT), Intensity Modulated Radiation Therapy (IMRT), or Stereotactic Body Radiation Therapy (SBRT).[28] Radioactive seed implantation is also called "brachytherapy."

Optimally, radiation therapy targets the cancer and tries to avoid the surrounding tissue and organs, namely the bladder, rectum, and the ureters that connect the kidneys to the bladder. These surrounding tissues may be affected, thus explaining the potential complications.

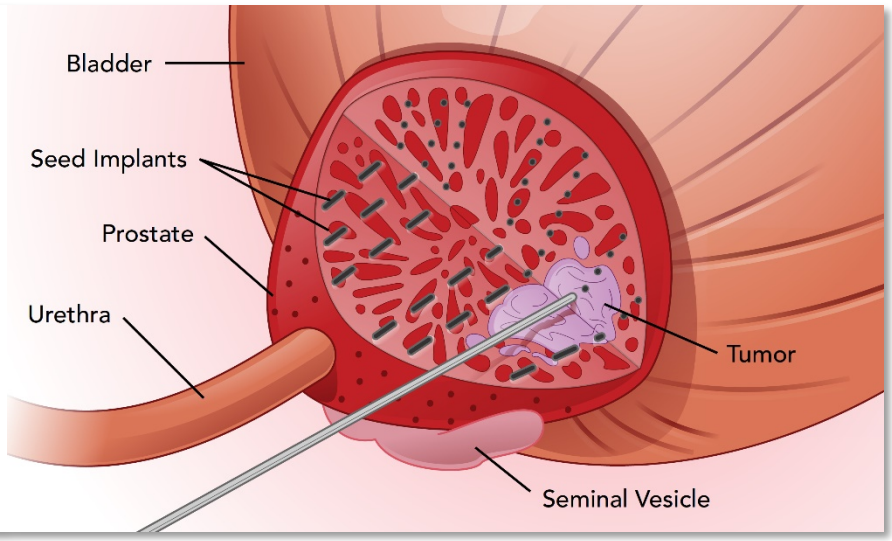
Brachytherapy (Seed Implant)

Permanent radioactive seed implantation (brachytherapy) is a good treatment option for some prostate cancer patients. Patients find this treatment very convenient, since it's a procedure that's done on an outpatient basis, with minimal recovery time, and does not require daily treatments over a long period of time. Although this is a good treatment option, it's not suitable for every patient. If patients do not urinate well and have significant lower urinary tract symptoms, seed implantation is not a good option. Also, if the prostate size is large (> 60 grams), the prostate may be too large for seed implantation. Some physicians have used short-term hormonal ablation therapy (temporary medical castration – see segment below) to shrink the prostate, but this generally will not improve lower urinary tract symptoms associated with an enlarged prostate. 5-alpha reductase inhibitors like finasteride (Proscar®) are sometimes also prescribed to help shrink the prostate. Seed implants are appropriate for patients who have low- to intermediate-risk prostate cancer who can urinate well without significant symptoms.

Seed implants are appropriate for patients who have low-risk to intermediate-risk prostate cancer who can urinate well without significant symptoms.

During brachytherapy, radioactive seeds are placed while the patient is under either spinal or general anesthesia. After anesthesia, the patient's legs are placed in stirrups and the prostate is imaged using transrectal ultrasonography. Needles are placed through a grid that sits on the perineum (the space between the scrotum and rectum) and has been mapped to correspond to the prostate. The small seeds are then placed through the needles starting at the base of the prostate and progressing out to the apex. Each seed can be seen on ultrasound to insure accurate placement.

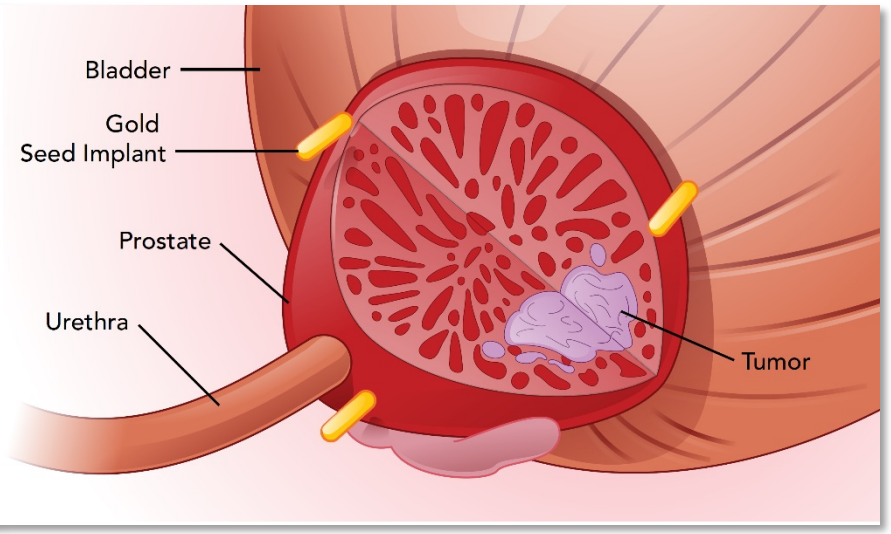
The radioactive seeds that are inserted in brachytherapy are smaller than a grain of rice.



If patients have more advanced disease, and are categorized as “high risk,” the effectiveness of seed implantation alone is not adequate. Most high-risk patients are treated with hormonal ablation therapy in combination with external radiation techniques.

Sometimes brachytherapy is combined with IMRT/IGRT, or brachytherapy and/or IMRT/IGRT are combined with hormone therapy. There are also instances in which all 3 are done (tri-modality). The side effects of tri-modality therapy may be higher than single-modality treatments.

Inserted gold seeds serve as markers to show exactly where the prostate is located.



Also, if a patient has too many medical problems, and is at high risk for anesthesia, then one might consider EBRT (see below). You will need to meet with a radiation oncologist who does seed implantation in order to see if you’re a candidate for a permanent radioactive seed implant.

External Beam Radiation Therapy (EBRT)

Standard forms of External Beam Radiation Therapy (EBRT) are:

- 3D conformal radiotherapy
- Image Guided Radiation Therapy (IGRT)
- Intensity Modulated Radiation Therapy (IMRT)
- Stereotactic Body Radiation Therapy (SBRT)

Treatments generally are given weekdays for 7-8 weeks. Before the therapy is started, 3 gold seeds are inserted – it's similar to having a biopsy. These seeds serve as markers that show exactly where the prostate is located; that's important because the prostate moves from one day to the next. The seeds ensure that the prostate is more accurately targeted and thus less radiation is administered to the surrounding tissues.

There are 3 common treatment durations, or number of treatments, that are used in EBRT:

- Conventional: For decades, radiation therapy has been delivered every day (Monday through Friday), for a total of 40 to 45 treatments over 8 to 9 weeks.

- Moderate hypofractionation: Clinical trials that have shown that as few as 20 treatments in 4 weeks can have similar cure rates and side effects as conventional radiation over 8 to 9 weeks. In hypofractionation, the doses given each day are higher than conventional dose levels.

- Ultra-hypofractionation: This is another name for SBRT, or treatment delivered in about 5 treatments. These doses are even higher than hypo fractionated doses. This strategy has lower side effects, equal cure rates, and increased convenience. However, not all patients are good candidates. This type of radiation has been shown to have similar cure rates and side effects compared to traditional 8 to 9-week course of radiation.

Proton Beam Radiotherapy

Protons are similar to photons (traditional x-ray radiotherapy) in many ways. However, proton beam therapy has not been shown to improve cure rates or quality-of-life outcomes over other forms of radiation therapy. There have been no completed head-to-head trials comparing proton beam radiotherapy to either surgery or traditional x-ray (photon) beam radiotherapy.

Hormone Therapy with Radiation

Hormone therapy is often given together with radiation therapy for localized disease and usually consists of a shot that lowers your testosterone, given every 1 to 6 months, depending on the formulation. Trials show a benefit in patients who receive hormonal treatment with radiation therapy. Hormone therapy has been shown to improve cure rates of prostate cancer for men receiving radiation therapy and is part of the standard of care for men with certain types of intermediate-risk prostate cancer and nearly all high-risk prostate cancer. It is often given for intermediate-risk cancer for 4 to 6 months (called short-term hormone therapy), and for 2 to 3 years in men with high-risk localized prostate cancer. Hormone therapy should not be given to men with low-risk prostate cancer and is not a standalone treatment for localized prostate cancer in any risk category.

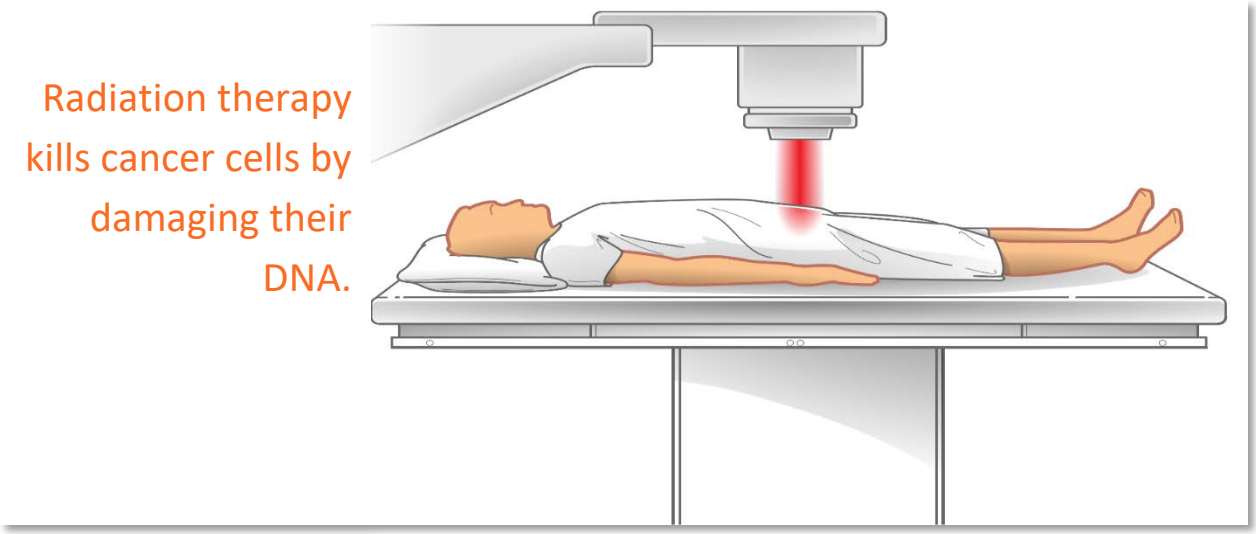
Complications of radiation therapy can be both short-term and long-term. Short-term complications may include:

- Fatigue
- Diarrhea
- Bleeding in the stool
- Painful bowel movements
- Urinary difficulty such as being unable to empty the bladder completely, pain with urination, urgency, and frequency

Long-term complications (even 10-20 years later) may include:

- Urinary difficulties
- Erectile dysfunction
- Bleeding in the urine or stool
- Blockage of the ureters
- Second malignancies of the bladder or rectum (rare)

Also, if a patient receives radiation and then requires surgery, such as a transurethral resection of the prostate (TURP) or “roto rooter,” to open the prostate channel to afford better urination, surgery can be more complicated, and healing inhibited. Lastly, if the radiation doesn’t eradicate the cancer, doing a radical prostatectomy is much more difficult and complicated. How do you know if radiation works? Again, PSA is used as a marker.



In response to radiation, PSA will drop. The lowest measurable level is called the PSA nadir. It is important to know that if hormone treatment is used as part of your treatment, the PSA nadir is defined as your PSA level after the hormone effect is gone and your testosterone level has returned to normal levels. A rise of PSA 2 points above nadir (PSA nadir +2) indicates a biochemical recurrence of cancer. When that happens, sometimes a repeat prostate biopsy is required to see if viable cancer is still within the prostate. Sometimes a bone scan, CT scan, PET scan, or MRI will be done.

Radiation may be a good treatment choice if you're older or have medical problems that would be made worse by having surgery.

Is radiation therapy right for you? It may be, it may not be. Again, it depends on a multitude of variables such as your general state of health, age, body shape and size, tumor grade and stage, overall size of the prostate, potency, previous surgeries, and more.

Every man with prostate cancer needs an individual assessment of these variables. What you desire with respect to outcome, risks, and complications needs to be considered. In some cases, surgery will offer a greater chance for cure. In other cases, there may be no difference in outcomes, that being survival with and without disease. The main difference in this case is what potential side effects and risks you are willing to accept.

Ablative Therapies

The last treatment for localized prostate cancer is called ablative therapies, which include cryotherapy and high intensity focused ultrasound (HIFU).[29]

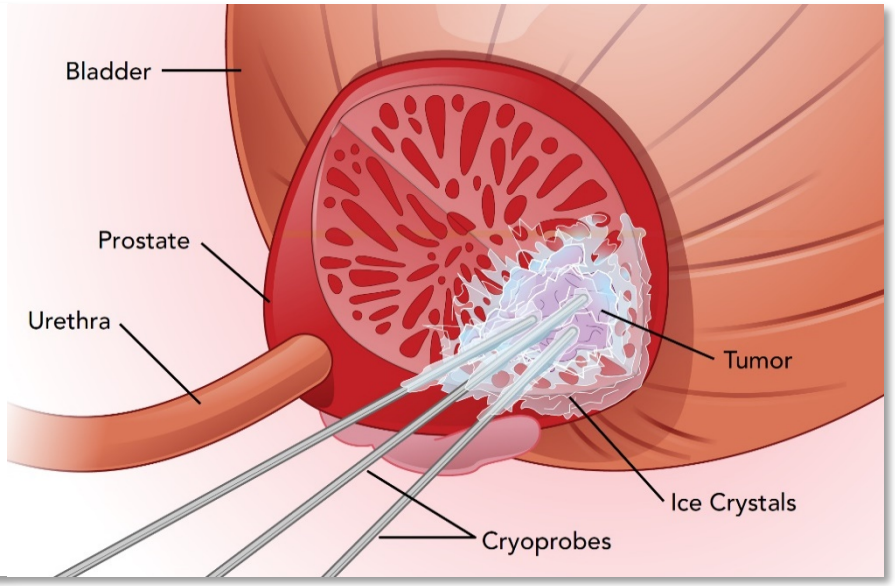
Cryotherapy

Cryotherapy, also known as cryosurgery or cryoablation, has been around for years, but is rarely used as the initial treatment for prostate cancer. This procedure involves controlled freezing of the prostate to very cold temperatures. Cancer cells, normal prostate cells and the small blood vessels that supply the prostate with nutrients and oxygen are frozen. The body's natural inflammatory system then comes in and cleans up the cellular debris. Scar tissue replaces the glandular and cancerous tissue of the prostate.

Cryotherapy is an outpatient procedure done under general or spinal anesthesia. Much like brachytherapy, the prostate is accessed via the perineum with the patient's legs raised and the feet often in stirrups (lithotomy position).

An ultrasound probe in the rectum maps the prostate. A computer generates a map, which is used to place the 6-8 cryoprobes, 5 needle thermometers (temp probes) that continuously monitor temperatures, and argon gas is delivered to the prostate, literally freezing the prostate cells to death.

Cryoablation offers controlled freezing to destroy cancerous cells.



Freezing of the prostate is even and complete. The temp probes monitor temperature in specific and critical areas in and around the prostate. A warming catheter in the urethra keeps the prostate lining warm and prevents internal damage to the urethra.

The procedure is done twice, followed by warming. At the end of the second thaw, a catheter is placed.

The patient is discharged on antibiotics, medication for pain and bladder spasms, and sometimes a drug called tamsulosin (Flomax®), which relaxes the smooth muscle where the bladder and prostate join. Tamsulosin will help voiding function a week later when the catheter is removed. Showers are allowed the next day, and activities can be resumed in as much as they are limited by the catheter.

A week later in the outpatient clinic a ***voiding trial*** is done. 10% of patients are unable to void a week later and are taught intermittent self-catheterization.

Rates for both erectile and urinary dysfunction remain high when cryotherapy is applied to the entire prostate, and data on long-term outcomes are limited.

In addition, a type of treatment referred to as “focal therapy,” which targets just a region of the prostate thought to have the tumor, instead of treating the entire prostate. These therapies have not been proven to have the same long-term success as surgery or radiation therapy, and thus are still considered experimental treatments. The likelihood of recurrence is higher with focal therapy due to the fact that in over 60% of cases, prostate cancer is actually “multi-focal,” meaning even if the biopsy and/or MRI showed the cancer to be in only one area, there is likely tumor in others areas of the prostate.

Cryotherapy has been typically used to treat patients who have failed radiation therapy for localized prostate cancer. This is called salvage cryotherapy. It is rarely recommended as primary treatment.

Immediate complications may include:

- Scrotal swelling
- Numbness in the head of the penis
- Blood in the urine
- Bladder spasms
- Burning in the urethra from the catheter
- Urinary retention can occur a week later when the catheter comes out

Later complications may include:

- Erectile dysfunction, which occurs in 50% of pre-cryoablation potent men
- Incontinence (less than 10% of the time)
- ***Urethral rectal fistula*** (less than 1% of the time)

High Intensity Focused Ultrasound (HIFU)

HIFU has been recently approved by the FDA for prostate tissue ablation **but is currently not FDA-approved for the treatment of prostate cancer and is thus experimental.**

HIFU works exactly the opposite of cryotherapy: with HIFU, 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. Side effects of HIFU are similar to those discussed above for cryotherapy and depend on the skill and experience of the surgeon using this technique. Serious side effects have also occurred after HIFU, despite it being "focal." Most of the published literature has demonstrated relatively high recurrence rates with HIFU.

Using HIFU to treat only the portions of the prostate thought to be cancerous instead of the entire prostate remains an area that is still being investigated.

Possible Side Effects Following Treatment

Prostate cancer and the associated treatments can disrupt normal urinary, bowel, and sexual functioning because the prostate is next to several important functional structures in the body.

Urinary Function

In order to control urination, the urinary sphincters (bands of muscle at the base of the bladder and at the base of the prostate) remain tightly shut preventing urine stored in the bladder from leaking out. The sphincters relaxed and the urine flows from the bladder through the urethra and out of the body during urination.

With the surgical removal of the prostate (prostatectomy), the bladder is pulled downward and connected to the urethra at the point where the prostate use to be. Almost all men will have some form of leakage immediately after the surgery, but this will improve over time and with strengthening exercises (Kegel). Pelvic floor muscle training with a physical therapist can help. The majority of men regain urinary control within a year; approximately 1 in 5 men will have mild leakage requiring the use of one or more pads per day. If incontinence persists past a year, a urethral sling or artificial urinary sphincter can potentially correct the leakage.

Radiation therapy is targeted to the prostate and it is directed away from the bladder and rectum. The urethra runs through the middle of the prostate, so it will receive radiation, but fortunately the urethra is very resistant to radiation therapy, and long-term urinary leakage is rare (less than 1 in 100). Although it can become irritated during treatment and for months after radiation therapy, resulting in an increase in urinary frequency and urgency. This can also cause waking up more at night to urinate (nocturia).

Bowel Function

As solid waste is excreted from the body, the resultant stool passes through the rectum and exits via the anus. Damage to the rectum can result in bowel problems, such as rectal bleeding, diarrhea, or urgency.

It very rare (less than 1%) for men to have altered bowel function after surgery to remove the prostate. For patients with locally advanced prostate cancer, where the

cancer invades the rectum, surgery may result in rectal damage, but surgery typically is not used in these types of cases.

Since the rectum sits underneath the prostate, it may also be exposed to radiation during radiation therapy. With modern radiation therapy, it is quite rare to have moderate or severe bowel problems (1%-3%). Some patients may experience softer stools or diarrhea (less than 10%) during radiation therapy, but these symptoms typically resolve within a few weeks after completing treatment. Bothersome rectal bleeding may occur months or years after treatment in 2% of men.

Fertility

After any prostate cancer treatment, you are unlikely to be fertile. The surgical removal of the prostate, seminal vesicles and part of the vas deferens disrupts the connection to the testes resulting in a vasectomy (sterilization). Orgasm may still occur (without ejaculation), but natural conception will not be possible. Radiation and ablative therapies similarly destroy the prostate and/or seminal vesicles; whereas chemotherapy and hormone therapy are both harmful to sperm production. If you are hoping to father a child in the future, fertility preservation and sperm cryopreservation should be discussed with your physician before you undergo any treatment.

Sexual Function

Erectile dysfunction remains the most common side effect after treatment regardless of whether the nerves were spared during surgery or whether the most precise dose planning was used during radiation. This is because the nerves and blood vessels that control your erections are very delicate and any trauma to the area can result in changes. The penis will look shorter, even when not erect because resting penile length still depends upon blood flow. Other less common side effects that can influence function include scarring in the penis (Peyronie's disease) and climacturia (releasing a small amount of urine during ejaculation). Fortunately, there are many treatment options that exist for managing erectile function. Most men with intact nerves will see a substantial improvement in erection function within 1 to 2 years after treatment.

It is important to understand that men with baseline erectile dysfunction and/or other diseases or disorders that impair the ability to maintain an erection, such as diabetes or vascular problems, will have a more difficult time returning to pre-treatment function. So, remember that your maximum functionality after treatment can only be as good as it was before treatment but in fact it is usually less.

Most men with localized disease treated surgically with what is termed a “nerve-sparing” prostatectomy. The goal of the procedure is to remove the prostate and seminal vesicles while leaving the nerves next to the prostate in place. Approximately 50%-60% of men who have the ability to have an erection before surgery will maintain this ability long-term. This number varies based on age, obesity, and the ability to spare the nerves based on the risk profile of your prostate cancer. If you receive radiation therapy after surgery, there will be a higher likelihood of erectile dysfunction since you are being exposed to the cumulative side effects of both treatments.

Damage to blood vessels and nerves after radiation therapy can result in decreased erectile function over time. Radiation therapy, in general, has less of an impact on erectile function in the first 5 to 10 years after treatment compared with surgery, and approximately 70% of men who have baseline erectile function before treatment will keep erectile function after treatment. However, radiation therapy has a slower delay in erectile function decline compared to surgery, and within 15 years after treatment, the rates are similar to those who underwent surgery.

Furthermore, these rates do not appear to be affected by the use of short-term (4 to 6 months) hormone therapy but are more likely to be affected by the use of long-term (18 to 36 months) hormone therapy.

Prior to undergoing treatment, it would be worthwhile to take the SHIM (Sexual Health Inventory for Men) test. Your score from this questionnaire will provide a documented and realistic baseline to which you might return to after surgery.

Lastly, one of the things to remember with all current erectile dysfunction treatments is that they are not curative, and they all provide varying degrees of temporary correction to the problem.

Detecting and Understanding Recurrence

PSA monitoring after treatment is an important way of understanding whether or not all the prostate cancer cells have been removed or destroyed. If you previously underwent surgery, your PSA should not be detectable after surgery.

If your PSA level begins to rise, your urologist will first try to determine where the PSA-producing cells are located. This may involve imaging, such as a CT or bone scan. However, in cases where PSA is still very low, imaging tests may not provide any information to determine a further course of action. Newer molecular imaging scans can also be done at the discretion of your urologist; these scans include C11-choline, F18-fluciclovine, F18-sodium fluoride (to evaluate for bone metastases, usually to confirm findings from bone scans) and PSMA-PET scans.

Following prostatectomy, PSA drops to “undetectable levels” (less than 0.1 ng/ml), whereas with radiation therapy, PSA level rarely drops to zero with this treatment because normal healthy prostate tissue isn’t always completely killed during radiation therapy. Instead, a different low point, called nadir, becomes the benchmark by which to measure a PSA rise. There are 2 different definitions for disease recurrence as measured by PSA following initial therapy with surgery or radiation therapy. Following prostatectomy, the most widely accepted definition of a recurrence is a confirmed PSA level ≥0.2 ng/mL. In the post-radiation treatment setting, the most widely accepted definition is a PSA rising from the lowest level (nadir) by at least 2.0 ng/mL.

Following radiation therapy, confirmation from multiple tests are needed because PSA can “bounce” or jump up for a short period and will later return to its low level. PSA bounces typically occur between 12 months and 2 years following the end of initial therapy.

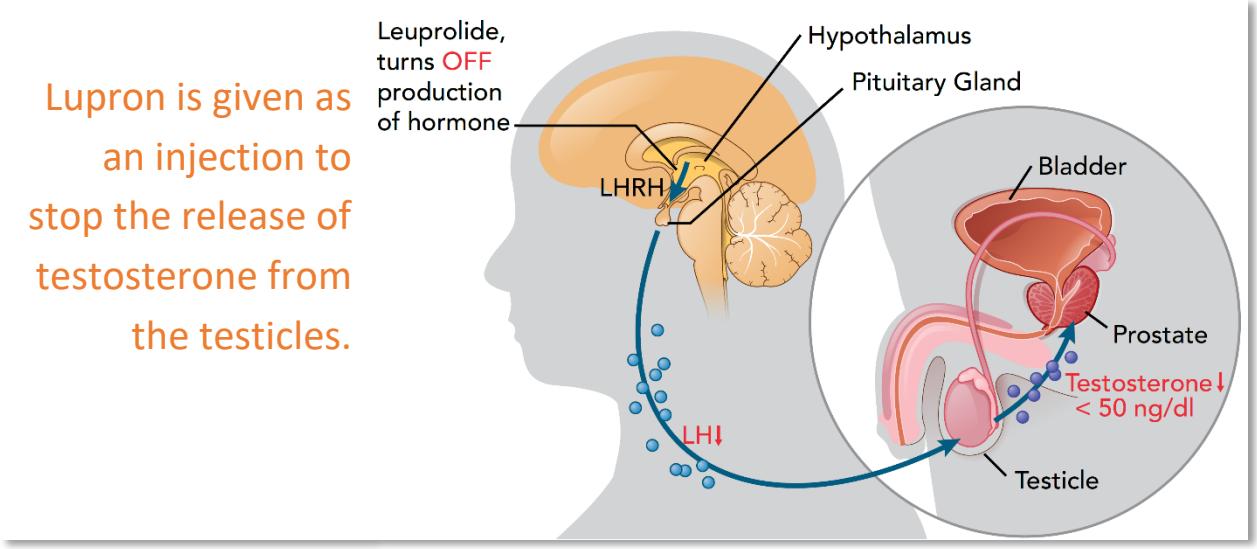
In general, the most common site of disease recurrence after surgery or radiation therapy is local, meaning within or near the prostate. For this reason, re-treating the prostate region may provide a second chance at cure. This secondary treatment is often referred to as “salvage” therapy. Your urologist will determine whether you would be a good candidate for a salvage therapy.

List of Salvage Therapies Available Depending upon your Initial Treatment

Surgery as initial treatment	Radiation as initial treatment
Radiation	Surgery
ADT	Brachytherapy
	Cryotherapy
	ADT

Hormone Therapy

The last topic we are going to discuss is hormone therapy. In 1941, Drs. Huggins and Hodges, from the University of Chicago, discovered that the growth of prostate cells, both benign and malignant, were governed by the male hormone, testosterone.[30] They discovered that, in dogs, if you take testosterone away by removing the testicles, the cells stop growing, shrivel up, stop making prostatic fluid, and in some cases, die. Dr. Huggins won the Nobel Prize for this work in discovering that prostate cancer is very dependent on male hormone.



Hormone therapy can be done by castration or by a long-acting drug that is injected intramuscularly.[31] One of these drugs is called Lupron (leuprolide). Lupron works in the part of the brain called the pituitary and causes a marked decrease in a hormone that stimulates the testicles to make testosterone. Think of a field of grass and weeds. The grass is normal cells and the weeds are cancer cells. Testosterone is fertilizer to both. Without it the grass and weeds will shrivel and stop growing. Lupron will significantly reduce testosterone levels but won't reduce them to zero; some testosterone (about 5%-10%) will continue to be made in the adrenal glands.

Another class of medications are first-generation "blocker drugs" or nonsteroidal androgen receptor antagonists include bicalutamide (Casodex®), flutamide (Eulexin®) and nilutamide (Anandron®, Nilandron®) that sit between testosterone and the cancer cell. Think of it like putting a barrier over the weeds so that the fertilizer can't get to them.

Even though 85% of prostate cancers are sensitive to hormone therapy, regrettably, no one is cured with this treatment. Whether or not survival is improved with hormone therapy is debatable. Eventually, hormone therapy fails to cure so-called “castrate resistant” cancer.

Side Effects of Hormone Therapy

Testosterone is the primary male hormone and plays an important role in establishing and maintaining typical male characteristics, such as body hair growth, muscle mass, sexual desire, and erectile function, and contributes to a host of other normal physiologic processes in the body. Androgen deprivation therapy (ADT), which lowers testosterone levels and causes side effects related to reversing all the normal functions of testosterone, in the primary systemic treatment for prostate cancer.

Although most men may experience only a few of these symptoms, the list of potential effects from testosterone loss is long: hot flashes (common), decreased sexual desire (common), loss of bone density and increased fracture risk (osteoporosis) (common), erectile dysfunction, fatigue, increased risk of diabetes and heart attacks, weight gain, decreased muscle mass, anemia, and memory loss. “Bad” cholesterol levels rise, particularly LDL and total cholesterol, and muscle tends to get replaced by fat, especially around the abdomen.

Changes in diet and exercise have been shown to relieve many of the side effects of ADT. Eating a heart-healthy diet low in red meat and high in vegetables and fiber and maintaining physical activity through daily weight-bearing exercise can reduce weight gain and maintain bone and muscle mass. There are also some strategies that can decrease the hot flashes, including medications and acupuncture. Lastly, it is important to check bone mineral density around the time of starting hormonal therapy and every 1 or 2 years following, to assess for loss of bone density. There are medications that can be used to reduce the risk of fracture if early signs of bone loss are found.

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Sounds pretty bad, doesn’t it? So why use it at all? Well, hormone therapy is usually reserved for men who have far advanced or metastatic disease. Those men are at significant risk for problems related to metastatic disease.

For example, in a patient with bone metastases, his bones are at great risk for fractures that we call pathologic fractures. If the bones of the spine are involved, the cancer can press on the spinal cord and lead to paralysis. Lymph nodes that are near the ureters (tubes that drain urine from the kidneys to the bladder) can enlarge from metastatic cancer and can block the flow of urine leading to kidney failure. Suffice it to say, the risks of not treating advanced or metastatic disease is greater than the risks of hormone therapy.

That's not the only reason we are talking about hormone therapy. There are occasions in which we want to shrink the prostate in order to enhance local therapy, as in the case of a man with the large prostate who chooses brachytherapy. There is also data to show that in a man with high grade and/or locally advanced cancer, adding hormone therapy to radiation therapy produces better outcomes than either alone.

It is also important to mention that hormone therapy alone is not an effective treatment strategy for men with localized prostate cancer. In fact, multiple large studies have shown that survival is worse with hormone therapy alone compared with hormone therapy with radiation therapy.[32-33] Of course, there are certain limited situations in which a patient's other illnesses, overall health status, or advanced age may make the use of ADT alone a consideration, but this is the exception rather than the rule.

Closing Thoughts

There is a lot here to digest. In closing, there are a few thoughts we'd like to leave you with:

1. Every man's cancer is different. Every prostate cancer is different. Every man with prostate cancer is different. Personal preferences, desires, and lifestyles are unique. Fears and concerns are different. Treatment plans need to be individualized.
2. Not all prostate cancers need to be treated. Active surveillance is a reasonable option for some men, but requires careful observation and follow-up, because 1 in 3 of patients who are candidates for active surveillance will progress to a more potentially dangerous cancer.
3. For some men for whom the potential benefits of ANY treatment outweigh the risks of NO treatment, no one treatment (surgery, radiation, or cryoablation) may be more advantageous than another. Survival outcomes with or without cancer will be similar. However, the potential risks and complications are quite different.
4. For some men, one therapy may have distinct advantages over the others, in spite of the differences in risks and complications.

Every man with prostate cancer is different. The type of treatment you choose is a matter of what risks you are willing to accept for what benefits.

Knowing as much as you can about your cancer will help you partner with your doctor in making an informed decision about the most appropriate treatment for you.

We hope this guidebook have given you enough information about prostate cancer to enable you to talk to your urologist, radiation oncologist, medical oncologist and primary care doctor. Together you will arrive at the right approach for you.

Glossary

Active Surveillance	An option for management of localized, low-risk prostate cancer. Various protocols that are institution specific exist and dictate how often and when repeat PSA blood tests and repeat follow up biopsies are done. Roughly 30% of men will “progress” to a potentially more dangerous cancer.
Anastomosis	A connection between two things. In the case of radical prostatectomy, it is the connection between the bladder neck and urethra.
Antegrade	The direction in which things go or flow. Antegrade flow is top to bottom, head to toe, north to south, or in the case of robotic retropubic prostate surgery, from the top of the bladder to the top of the prostate. The opposite of antegrade is retrograde. In an open radical prostatectomy or perineal (the space between the scrotum and rectum) prostatectomy, the dissection is retrograde.
Benign prostatic Hyperplasia	Benign, non-cancerous enlargement of the prostate that occurs as men get older, starting in the 5th decade of life. The enlargement can squeeze or block the urethra resulting in a variety of urinary symptoms.
Biochemical/PSA Recurrence	After complete surgical removal of the prostate, all PSA producing cells, both cancer cells and benign prostate cells are removed. When all the cancer and prostate are removed, then PSA drops to undetectable levels. If the PSA becomes detectable and starts going up after surgery, this is referred to as biochemical recurrence. Since the prostate remains in after radiation therapy (all types), cryoablation, and hormone therapy, there can still be detectable levels of PSA in patients who are cured and never have a recurrence. After these therapies, the lowest level of PSA is called the nadir. There are criteria for biochemical recurrence in patients who have been treated by methods other than surgery. The most common criteria that define biochemical recurrence is nadir PSA level plus 2 points (i.e., if nadir PSA level is 1.2, a failure is at a PSA level of 3.2).

Brachytherapy	A form of radiation therapy in which radioactive seeds about the size of a small grain of rice are placed into the prostate.
CT or CAT scan	Computerized axial tomography, imaging based on a series of x-rays fed into a computer that generates cross sectional images.
Cancer grade	A description of a tumor based on what the architecture of the cells and how abnormal the cells appear under the microscope. Grading systems are different for different types of cancer. The grading system for prostate cancer was developed by Dr. Donald Gleason, a pathologist from Minnesota who died at the age of 88 from a heart attack.
Cancer-free survival	Survival without biochemical recurrence and no evidence of prostate cancer anywhere else. Different from another statistic called overall survival which is the sum of patients alive with and without prostate cancer following treatment or active surveillance.
Clinical cancer stage	Refers to whether or not the tumor can be felt on digital rectal exam; the extent to which the suspected tumor can be seen on imaging studies (though these studies are not very accurate sometimes); how big the suspected tumor is; how much of the prostate is occupied by the lump or nodule; is it in one or both lobes; can it be felt outside the prostate; can it be felt in the seminal vesicles (see definition below); is the prostate mobile on exam or fixed; and can it be detected by imaging or scans (bone, CT, MRI) in lymph nodes, bones, or other organs.
Extracapsular extension	If the capsule is like the rind of an orange, and the pathologist sees cancer outside of the rind, then there is extracapsular extension. The radiologist or urologist may suspect extracapsular extension on CT, MRI, or ultrasound, but these tests are not very accurate, though the accuracy is improving with technological innovations and greater experience.
Gleason grade	See cancer grade above. A score of 3, 4, or 5 is assigned based mainly how abnormal looking the cancerous glands in the prostate are arranged.

Gleason score	Each biopsy specimen may contain one, two, or three grades (3, 4, or 5). The score is the most commonly seen grade plus the second most common grade. An example would be a biopsy sample that is composed of 80% Gleason 3 cancer and 20% Gleason 4. The Gleason score would be 3+4 or 7. If, for example, the situation was reversed and there was 80% Gleason 4 and 20% Gleason 3, the score would still be 7, but the pathologist would report it as 4+3. The distinction is important because a Gleason 3+4 tumor is potentially less aggressive than a 4+3, even though the score is 7 in each case.
Hyperlipidemia	The presence of excess fat or lipids in the blood.
IGRT (Image Guided Radiation Therapy)	A form of external beam radiation therapy during which 2- and 3- dimensional images are used to guide the radiation beams to hit the prostate and minimize radiation to surrounding structures and organs.
IMRT (Intensity Modulated Radiation Therapy)	An advanced form of 3-dimensional external beam therapy using computer software and hardware designed to get maximal radiation to the prostate while at the same time minimal dose to surrounding structures and organs.
Interstitial	The technical definition is “between spaces or interstices” but for our practical purposes it means something put into the tissue of the prostate.
Lymph nodes	The lymphatic system filters the plasma in blood. Lymph channels are like small blood vessels that follow along the course of most of the blood vessels in your body. Nodes are swollen areas of tissue that help with the filtering. Cancer cells can spread via blood or lymph channels. When the cancer is in the node, it can grow and cause lymph node enlargement. This is referred to as “lymph node metastases.”
MRI (Magnetic Resonance Imaging)	Uses magnetic fields and radio waves to produce images of structures inside the body. These pictures can provide different information of the same structures seen on CT, Ultrasound, or traditional x-rays.

Metastases	Any cancerous growth that appears beyond the site of the original cancer site. Prostate cancer seen in lymph nodes, bones, liver, lung, or other organs, is metastatic.
Neurovascular bundle	A group of nerves, arteries, and veins that travel along each side of the prostate (outside of, but adherent to, the prostate capsule) and support the prostate, urethral (external) sphincter (see below), and penis. A “nerve sparing prostatectomy” dissects this bundle off the prostate on one side or both to enhance chances of recovery of erectile function after surgery.
Nomogram	A prediction tool that uses several pieces of clinical information to better determine the aggressiveness of the cancer. Some of the information might include: your PSA level, the grade of the cancer on biopsy, the clinical stage, how many needles showed cancer, etc. The nomogram can help decide which option or treatment will provide the greatest benefit.
Palpable	Felt by touch.
Prostatitis	Infection or inflammation of the prostate. Either can cause an elevated PSA in the absence of cancer.
Radical Prostatectomy	Surgery to remove the prostate and seminal vesicles.
SEER (Surveillance Epidemiology End Result Program)	SEER is an authoritative source of information on cancer incidence and survival in the United States. SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 28% of the U.S. population.

Seminal vesicles	Glands that produce seminal fluid, which makes up 95% of semen (the other 5% is sperm from the testes). Seminal vesicles are two glands located behind the bladder, above the rectum, and attached to the base of the prostate (just under where the bladder and prostate attach). They are removed along with the prostate during surgery (radical prostatectomy). Prostate cancer can spread to these glands.
Sphincter	There are two for our purposes, but others in the body also. Sphincters are a ring of muscle that surround an outlet, opening, or tube. During voiding, urine passes through two sphincters, the internal, where the bladder and prostate join, and the external, which is on the penis side of the prostate. After the prostate is surgically removed, the internal sphincter may no longer be functional or it may be weaker, and continence (the ability to hold urine in, stay dry, or not leak) depends more on the function and competence of the external sphincter.
Ureters	Hollow tubes or ducts that drain urine from each kidney to the bladder.
Urethra	Another hollow tube that originates at the bladder neck, passes though the prostate like a drinking straw through an orange, through the external sphincter, and then through the penis. Urine passes through this tube during urination. It is also the tube through which a catheter is passed into the bladder.
Urethral Rectal Fistula	An abnormal passageway or connection between the urethra and rectum following radiation, cryotherapy, or even surgery. It's a two-way street – urine goes into the rectum and feces gets into the urine. Fortunately, this is a very rare complication after all treatments. Symptoms include passage of air, blood, or feces in the urine. Urinary tract infections are common and difficult to treat. Surgery is frequently necessary to repair the fistula.

Voiding Trial	After any of the treatments, your doctor wants to be sure you will be able to urinate so he/she may do a voiding trial. The bladder is filled by running water, saline, or occasionally x-ray dye, through the catheter (which is still in after surgery, brachy or cryo, or had to be placed during or after external beam therapy because of significant voiding difficulty). When the patient feels full, the catheter is removed and the patient is allowed to urinate. The amount of fluid left still in the bladder after voiding can be measured with a simple bladder scanner ultrasound or seen on x-ray if dye is used. If dye is used, sometimes small leaks from the anastomosis (see above) can be seen.
Watchful Waiting	Since many small or localized or low-risk prostate cancers are not likely to harm elderly men (older than 70-75), this is a less intensive method of monitoring patients than active surveillance. There is less agreement among urologists with regard to the definition of this term and how it is different than active surveillance. So, if your doctor uses this term, be sure to have him/her explain what he/she means by it, and how it differs from active surveillance.

Reference List

1. Prostate Cancer - Cancer Stat Facts. National Cancer Institute: Surveillance, Epidemiology, and End Results Program. https://seer.cancer.gov/statfacts/html/prost.html. Accessed April 10, 2020.f

2. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. *J Clin Oncol*. 2015;33(3):272-277. doi:10.1200/JCO.2014.55.1192

3. Dall'Era MA, Konety BR, Cowan JE, et al. Active surveillance for the management of prostate cancer in a contemporary cohort. *Cancer*. 2008;112(12):2664-2670. doi:10.1002/cncr.23502

4. Bul M, Zhu X, Valdagni R, et al. Active surveillance for low-risk prostate cancer worldwide: the PRIAS study. *Eur Urol*. 2013;63(4):597-603. doi:10.1016/j.eururo.2012.11.005

5. McNeal JE. Normal histology of the prostate. *Am J Surg Pathol*. 1988;12(8):619-633. doi:10.1097/00000478-198808000-00003

6. McVary KT, Roehrborn CG, Avins AL, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. *J Urol*. 2011;185(5):1793-1803. doi:10.1016/j.juro.2011.01.074

7. Walz J, Graefen M, Huland H. Basic principles of anatomy for optimal surgical treatment of prostate cancer. *World J Urol*. 2007;25(1):31-38. doi:10.1007/s00345-007-0159-6

8. Wang G, Zhao D, Spring DJ, DePinho RA. Genetics and biology of prostate cancer. *Genes Dev*. 2018;32(17-18):1105-1140. doi:10.1101/gad.315739.118

9. Gartrell BA, Coleman R, Efstathiou E, et al. Metastatic Prostate Cancer and the Bone: Significance and Therapeutic Options. *Eur Urol*. 2015;68(5):850-858. doi:10.1016/j.eururo.2015.06.039

10. Gandaglia G, Abdollah F, Schiffmann J, et al. Distribution of metastatic sites in patients with prostate cancer: A population-based analysis. *Prostate*. 2014;74(2):210-216. doi:10.1002/pros.22742

11. Makarov DV, Carter HB. The discovery of prostate specific antigen as a biomarker for the early detection of adenocarcinoma of the prostate. *J Urol*. 2006;176(6 Pt 1):2383-2385. doi:10.1016/j.juro.2006.08.019

12. Carter HB. Prostate Cancers in Men with Low PSA Levels — Must We Find Them? *N Engl J Med*. 2004;350(22):2292-2294. doi:10.1056/NEJMe048003

13. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. *J Urol*. 1974;111(1):58-64. doi:10.1016/s0022-5347(17)59889-4

14. Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. *Am J Surg Pathol*. 2016;40(2):244-252. doi:10.1097/PAS.0000000000000530

15. Mohler JL, Srinivas S, et al. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Prostate Cancer (Version 1.2020). National Comprehensive Cancer Network. www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Published March 16, 2020. Accessed April 10, 2020.

16. Caras RJ, Sterbis JR. Prostate cancer nomograms: a review of their use in cancer detection and treatment. *Curr Urol Rep*. 2014;15(3):391. doi:10.1007/s11934-013-0391-0

17. Partin AW, Yoo J, Carter HB, et al. The use of prostate specific antigen, clinical stage and Gleason score to predict pathological stage in men with localized prostate cancer. *J Urol*. 1993;150(1):110-114. doi:10.1016/s0022-5347(17)35410-1

18. Kattan MW, Eastham JA, Stapleton AM, Wheeler TM, Scardino PT. A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. *J Natl Cancer Inst*. 1998;90(10):766-771. doi:10.1093/jnci/90.10.766

19. Cucchiara V, Cooperberg MR, Dall'Era M, et al. Genomic Markers in Prostate Cancer Decision Making. *Eur Urol*. 2018;73(4):572-582. doi:10.1016/j.eururo.2017.10.036

20. Lin DW, Zheng Y, McKenney JK, et al. 17-Gene Genomic Prostate Score Test Results in the Canary Prostate Active Surveillance Study (PASS) Cohort. *JCO*. March 2020:JCO.19.02267. doi:10.1200/JCO.19.02267

21. Glass AS, Dall'Era MA. Indications for and transitioning to secondary treatment while on active surveillance for prostate cancer. *Transl Androl Urol*. 2018;7(2):236-242. doi:10.21037/tau.2018.02.08

22. Wroński S. Radical perineal prostatectomy - the contemporary resurgence of a genuinely minimally invasive procedure: Procedure outline. Comparison of the advantages, disadvantages, and outcomes of different surgical techniques of treating organ-confined prostate cancer (PCa). A literature review with special focus on perineal prostatectomy. *Cent European J Urol*. 2012;65(4):188-194. doi:10.5173/ceju.2012.04.art2

23. Lowrance WT, Eastham JA, Savage C, et al. Contemporary open and robotic radical prostatectomy practice patterns among urologists in the United States. *J Urol*. 2012;187(6):2087-2092. doi:10.1016/j.juro.2012.01.061

24. Walsh PC. Anatomic radical prostatectomy: evolution of the surgical technique. *J Urol*. 1998;160(6 Pt 2):2418-2424. doi:10.1097/00005392-199812020-00010

25. Williams SB, Prasad SM, Weinberg AC, et al. Trends in the care of radical prostatectomy in the United States from 2003 to 2006. *BJU Int*. 2011;108(1):49-55. doi:10.1111/j.1464-410X.2010.09822.x

26. Novara G, Ficarra V, Mocellin S, et al. Systematic review and meta-analysis of studies reporting oncologic outcome after robot-assisted radical prostatectomy. *Eur Urol*. 2012;62(3):382-404. doi:10.1016/j.eururo.2012.05.047

27. Coughlin GD, Yaxley JW, Chambers SK, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: 24-month outcomes from a randomised controlled study. *Lancet Oncol*. 2018;19(8):1051-1060. doi:10.1016/S1470-2045(18)30357-7

28. Martin NE, D'Amico AV. Progress and controversies: Radiation therapy for prostate cancer. *CA Cancer J Clin*. 2014;64(6):389-407. doi:10.3322/caac.21250

29. Ramsay CR, Adewuyi TE, Gray J, et al. Ablative therapy for people with localised prostate cancer: a systematic review and economic evaluation. *Health Technol Assess*. 2015;19(49):1-490. doi:10.3310/hta19490

30. Huggins C, Hodges CV. Studies on Prostatic Cancer. I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate. *Cancer Res*. 1941;1(4):293-297.

31. Hahn AW, Higano CS, Taplin M-E, Ryan CJ, Agarwal N. Metastatic Castration-Sensitive Prostate Cancer: Optimizing Patient Selection and Treatment. *Am Soc Clin Oncol Educ Book*. 2018;38:363-371. doi:10.1200/EDBK_200967

32. Lu-Yao GL, Albertsen PC, Moore DF, et al. Survival Following Primary Androgen Deprivation Therapy among Men with Localized Prostate Cancer. *JAMA*. 2008;300(2):173-181. doi:10.1001/jama.300.2.173

33. Schmidt-Hansen M, Hoskin P, Kirkbride P, Hasler E, Bromham N. Hormone and radiotherapy versus hormone or radiotherapy alone for non-metastatic prostate cancer: a systematic review with meta-analyses. *Clin Oncol (R Coll Radiol)*. 2014;26(10):e21-46. doi:10.1016/j.clon.2014.06.016