STAGING GUIDE

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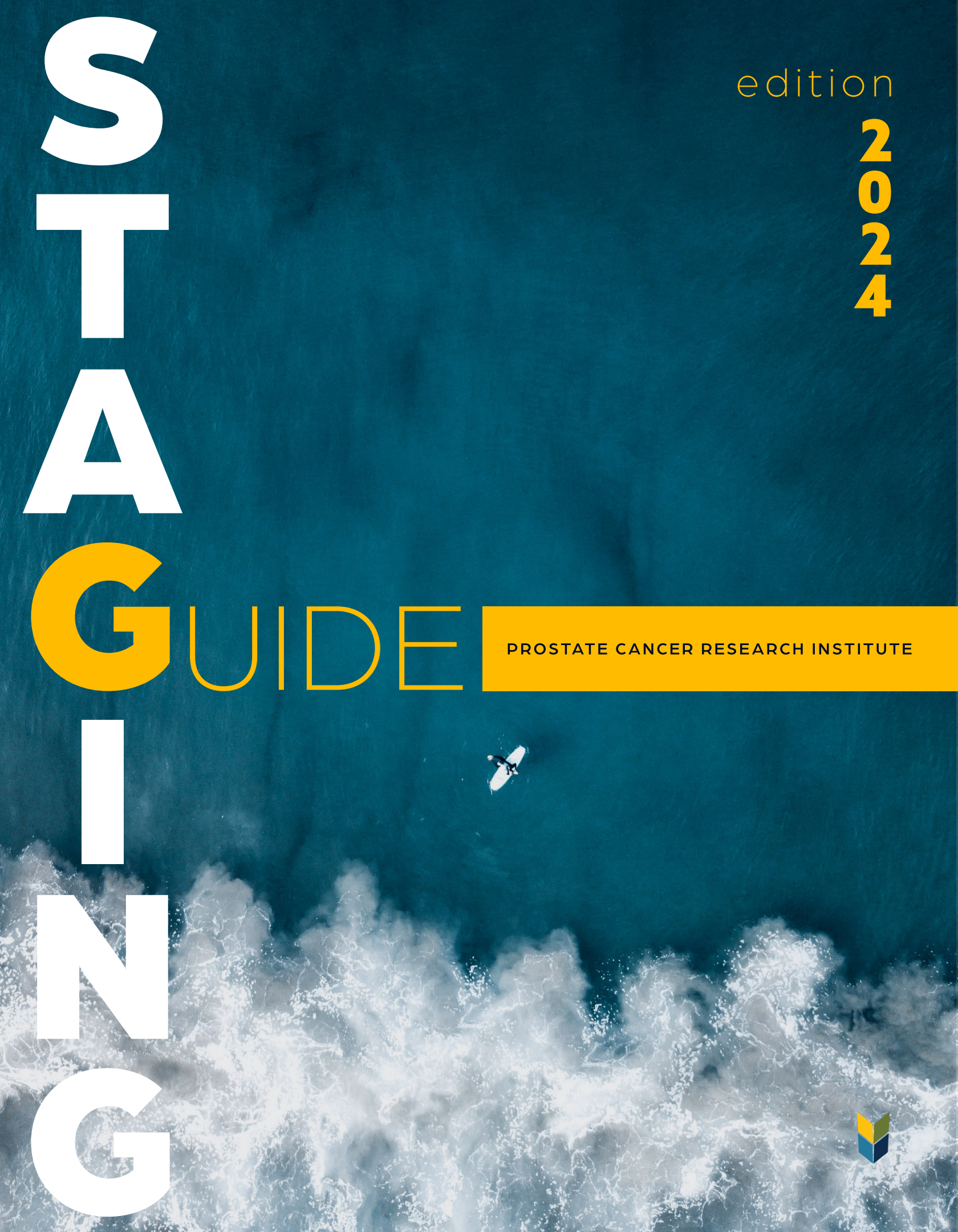
PROSTATE CANCER RESEARCH INSTITUTE



PREFACE

"Prostate Cancer" is a nonspecific and very ambiguous umbrella term.

After a diagnosis of prostate cancer, men need more precise specifics about their situation to get a handle on what's going on. Is this an innocuous and irrelevant growth (Gleason 6); or are they facing life-threatening metastases? The PCRI recommends conceptualizing prostate cancer in five major categories by integrating PSA, biopsy information, physical examination and scans. Three of these "stages" are in men who are newly diagnosed: Low-Risk, Intermediate-Risk, and High-Risk which the PCRI calls Sky, Teal, and Azure. The other two stages, Indigo and Royal, represent relapsed disease and metastatic disease, respectively.

To find your stage take the quiz in Chapter 1. As you delve into this website deeply, you will find that there are three subtypes in each stage, each one of which behaves in a distinct fashion and requires different treatment. Therefore, prostate cancer, having five stages, each with three subtypes, is made up of 15 diverse subtypes.

Knowing your stage, where you stand in the prostate cancer universe, offers many benefits:

1. It shows you where to begin your research.
2. It prevents you from being side-tracked by irrelevant information.
3. It points you toward the best treatment options for your type of prostate cancer.
4. It brings you up to speed on how doctors think about your specific type of prostate cancer.
5. It elevates your knowledge, enabling you to converse on more equal terms with your doctor, enabling you to participate in a shared decision-making process.

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Introduction

Once the proper Stage of Blue is assigned (Chapter 1), the different treatments appropriate for that Stage can be considered and compared. In the prostate cancer treatment realm, decisions are usually based on comparisons amongst several alternatives. In the most general sense, there are four main types of treatment: observation, local treatments, systemic treatments, and combination therapy.

Observation

Observation, commonly known as "active surveillance," is the process of monitoring the cancer while reserving medical intervention until some aggressive behavior is detected.

Local Treatments

Strategies that focus on treating the prostate gland are called "local" treatments. Examples are surgery, radioactive seed implantation, varieties of external beam radiation therapy (IMRT, Proton, SBRT), and cryosurgery. In addition, "focal" treatment options have been developed in which only a subsection of the gland is treated.

Systemic Treatments

The main danger from prostate cancer is the possibility of cancer spreading outside the prostate. Men with metastases (or potential microscopic metastases) require systemic treatment that circulates through the blood and treats cancer throughout the whole body. Examples of systemic treatments are hormonal therapies, chemotherapy, immunotherapy, and systemic targeted radiation.

Combination Therapy

When a local treatment is combined with a systemic treatment, or if multiple systemic treatments are used at the same time, it is called "combination therapy." As is the case when contemplating any form of treatment, when combination therapy is being considered, the purported survival advantages need to be balanced against the impact on quality of life.

CHAPTER 1

Accessing the Medical Chart to Assign a Stage of Blue

Many treatments have irreversible consequences, so the goal is to do it right the first time. It is well known that long-term survival is improved by receiving optimal treatment up front. The first treatment is your best opportunity to eradicate cancer. The initial step in the treatment selection process is to determine your Stage of Blue, to know as precisely as possible what it is exactly that you are treating.

First, obtain a copy of your medical records. You have every right to obtain and keep your records. Some offices may charge a small fee for providing you with the records. There is no universal format for charts, and some offices keep more complete records than others. It may be necessary to request information from more than one doctor's office to compile all the necessary information. You don't need a complete understanding of everything in the chart. However, there are certain specific items you need to look for:

Prostate Specific Antigen (PSA) Chronology: Construct a chronological history of every PSA measurement that has ever been taken and the date that it was performed. The PSA results can be found in your Lab Reports. The testosterone level is also found in this section of the chart.

Clinical Stage: Information about the digital rectal examination (DRE) will be found in the Progress Notes section of the chart. Results indicate whether a nodule can be felt by the doctor's finger. The type of nodule that is felt is recorded as the "T" stage. The doctor records his impression of the DRE in the Physical Examination section of the Progress Notes section of the chart per the following table:

T1: No tumor is felt
T2: Tumor feels confined within the prostate
T2a: Tumor that can be felt but involves 50% or less of one lobe
T2b: Tumor felt involving more than 50% of one lobe but not both lobes
T2c: Tumor felt in both lobes
T3: Tumor felt that extends through the prostate capsule
T3a: Extracapsular extension is felt
T3b: Tumor felt that invades seminal vesicle(s)
T4: Tumor felt that invades rectum or bladder

Radiology Reports (imaging studies): The radiology reports will be found in the Radiology section of the chart. Look for the Impression section of the report where the doctor who wrote the report summarizes the essential aspects of the scan results.

Biopsy Report: The biopsy report will be in the Pathology section of the chart. For each of the biopsy cores that contain cancer, you should make note of the Gleason score and the percentage of the core that contains cancer.

Finding Your Stage of Blue with The Quiz

The above information from your medical chart provides the data required to assign a Stage of Blue. The formula calculates your Stage by summing up the numbers written in response to the questions in the following two Quizzes:

Quiz A

Question 1: Have you had surgery, radiation, or cryotherapy for prostate cancer and now have persistent cancer or a rising PSA? If no, continue to question 2; if yes, skip to Quiz B (see below).

Question 2: Do you have a pathology report or a Bone, PET, CT, or MRI scan that shows any bone metastases or metastases in lymph nodes located outside the pelvis area of the body? If yes, skip to Quiz B. If no, or if the metastases are located exclusively in the lymph nodes in the pelvis area, continue to question 3.

Question 3: #_____ What was your PSA at the time of your diagnosis?
a. Less than 10 ng/ml (write #1)
b. More than 10 but less than 20 ng/ml (write #2)
c. More than 20 ng/ml (write #5)

Question 4: #_____What was the highest Gleason score on your biopsy?
a. 6 or less (write #1)
b. 7 (write #2)
c. 8 or more (write #5)

Question 5: #_____What "T" stage does your digital rectal exam (DRE) show? (See the table on the previous page in the clinical stage section to understand "T" stage)

a. Small or no nodule (T1c, T2a) (write #1)
b. Larger nodule (T2b) (write #2)
c. Bilateral nodule or extracapsular extension (T2c, T3, T4) (write #5)

Question 6: #_____ Do you have an MRI, color Doppler, or PET/CT Scan showing cancer outside the prostate?

a. No extracapsular extension (write #0)
b. Overt extracapsular extension (write #3)
c. Seminal vesicle invasion (write #4)
d. Abnormal pelvic nodes (write #4)

Write the total of questions 3 through 7 _____. Your Stage of Blue is indicated by the sum:

3 = Sky 4–6 = Teal 7+ = Azure

Quiz B:

Use the following three questions to determine your Stage of Blue.

Question 1: #_____Is your current PSA

a. Less than 100 (write #0) b. More than 100 (write #1)

Question 2: #_____Do you have a rising PSA and a low testosterone under 50?

a. No (write #0) b. Yes (write #1)

Question 3: #_____Does an MRI, PET/CT, bone scan or surgery show any metastases beyond the pelvic nodes?

a. No (write #0) b. Yes (write #1)

Write the sum of these three questions here: #_____ Your Stage of Blue is indicated by the sum:

0 = Indigo 1+ = Royal

The five chapters that follow explain the basic components of the Stages of Blue—PSA, Gleason score, prostate scans, and body scans. Although the Stages of Blue can serve you perfectly well without all these background fundamentals, the goal of this book is to introduce basic vocabulary and thought processes that are utilized throughout the prostate cancer world. Becoming familiar with this information will take the level of conversation with your doctor to a higher level.

CHAPTER 2

The PSA Blood Test

PSA plays a variety of roles, the most familiar being screening to detect prostate cancer. PSA also helps to define the Stages of Blue. Another role of PSA is to detect cancer relapse after surgery or radiation. Lastly, rises or declines in PSA after hormone therapy or chemotherapy help determine whether a treatment is working or not.

Prostate Cancer Screening is Controversial

PSA screening often leads to the detection of small, essentially harmless cancers. Doctors and patients frequently overreact, rushing into unnecessary radical treatment. Overtreatment of tiny cancers became such a big problem that in 2011 a government-sponsored team of experts, the U.S. Preventive Services Task Force, issued a warning against routine PSA screening. This recommendation was recently rescinded, acknowledging the value of PSA screening in well-informed patients.

Scans Measure the Size of the Prostate

Imaging with ultrasound or MRI improves the accuracy of PSA. Let me explain why. Many men run high PSA levels from a condition called BPH that is totally unrelated to cancer, creating concerns that prostate cancer might be present. However, BPH is benign enlargement of the prostate gland, a common phenomenon associated with aging that is unrelated to prostate cancer.

The formula for determining when the PSA is outside the range expected when the enlarged gland is taken into account is as follows: PSA is "normal" when your PSA is approximately the same number as when your prostate volume is divided by 10. For example, a noncancerous 30cc prostate should have a PSA of around 3.0; for a noncancerous 50cc prostate the PSA should be around 5.0. A man's PSA with a 100cc prostate will be approximately 10. PSA is only abnormal (the official term is a "high PSA density") when it's 50 percent higher than would be expected, based on the prostate's size. For example, a man's PSA is abnormal if he has a 30cc prostate and his PSA is above 4.5. An abnormal PSA for a 50cc prostate is above 7.5. For a 100cc gland, PSA would need to be above 15 to be suspicious.

PSA Density

Doctors use a less intuitive way to do the exact same calculation. Instead of dividing PSA into the gland volume, they do the opposite. They divide the gland volume into the PSA. Using this inverted formula, an abnormal PSA relative to a specific-sized prostate is anything above 0.15. Men above 0.15, using this formula, are said to have a high "PSA Density."

A Suggested PSA Screening Protocol

PSA is inexpensive and easily accessible. Therefore, it is reasonable to start checking PSA in men over the age of 40. The only precaution is to go slow and do careful research about next steps if the PSA is found to be elevated

Using PSA to Stage Prostate Cancer

Despite the controversies that surround the use of PSA for screening, there are no controversies about using PSA for cancer staging. Men with a higher PSA at the time of diagnosis, above 10 or 20 for example, are more likely to have cancer that has spread outside the gland. The exact methodology for determining a man's Stage of Blue, using PSA in combination with other factors, is explained in Chapter 1.

PSA to Monitor for Cancer Relapse After Local Therapy

Cancer recurrence can be signaled by a rising PSA. Normally after surgery,the PSA should drop to undetectable levels. Even a small rise in PSA is significant. After radiation, the PSA should generally remain well below 1.0. When there is a cancer recurrence after previous surgery or radiation, the rate of PSA doubling is a very important indicator of the recurrent cancer's aggressiveness. For example, recurrences associated with PSA levels that require over 12 months to double are low-grade. On the other hand, a PSA that doubles in less than three months signals aggressive disease.

PSA to Determine the Response to Systemic Therapy

A PSA decline of more than 30 percent within a couple of months of starting chemotherapy provides a strong indication that the treatment is working. However, not every treatment, even when it is effective, makes an impact on PSA. Two therapies for Royal—Xofigo and Provenge—clearly prolong life but may show little or no impact on PSA.

Conclusion

PSA results must be utilized in the context of each patient's overall circumstanc-es by an expert with experience in managing prostate cancer. Unexpected PSA results should always be retested. Laboratory errors are possible, and variations also occur between labs.

CHAPTER 3

Interpreting the Pathology Report and Gleason Score

The two major components of the pathology report from a random 12-core biopsy are the Gleason score, which measures how aggressive the tumor appears, and the quantity of cancer, i.e., the extent of disease detected by the 12-core specimen.

What Is The "Gleason Grade" Or "Gleason Score"?

The Gleason grading system assigns a "pattern" to the cancer cells, depending upon their appearance under the microscope. The patterns are graded from 1 to 5. The pathologist assigns a higher number when the appearance of the cancer cells deviates more from the visual appearance of normal prostate gland tissue. The first number in the score is the grade that applies to the most common type of cancer seen in the biopsy. The second number in the score is the next most common grade. These two different grades are then added together to yield the Gleason score. In actual practice, the Gleason score only ranges between 6 and 10. Therefore, a Gleason 6 is the lowest, most favorable grade possible.

What Does It Mean to Have a Gleason Score of 7?

A Gleason score of 7 can mean 3+4=7 or 4+3=7, depending on whether grade 3 pattern or grade 4 pattern is predominant. The biggest therapeutic difference between these grades is that more aggressive radiation therapy protocols are often recommended for Gleason scores of 4+3=7 and higher.

What Does It Mean to Have Gleason Scores of 8 to 10?

Gleason score 8 cancers are relatively more aggressive, and Gleason score 9 to 10 cancers are more so. However, most patients with Gleason scores 9 or 10 can still be cured. The actual outlook for a specific patient also depends on additional factors, such as PSA, clinical stage, and the extent of cancer in and outside the prostate.

Can the Biopsy Gleason Score Determine the Grade in the Entire Prostate?

The Gleason score obtained via a random biopsy usually reflects the cancer's true grade. However, in about 25 percent of cases the biopsy underestimates the true grade, resulting in under-grading. Somewhat less commonly, over grading occurs. This occurs when the true grade of the tumor is lower than that which is seen in the biopsy.

How Can Patients Be Sure the Reported Gleason Grade Has Been Read Correctly?

How accurately a pathologist assigns a Gleason score depends on his training and experience. If you are uncertain about the pathologist's credentials, it may be prudent to submit the biopsy material for a second opinion to a center managing large numbers of patients with prostate cancer, to confirm the accuracy of the initial Gleason score.

CHAPTER 4

Prostate MRI and Targeted Biopsy

Multiparametric MRI (MRI) provides a three-dimensional image of the prostate, giving important information about the cancer's location, size, and how "aggressive" it appears. MRI also greatly increases the confidence that higher-grade cancers are not being overlooked in men on active surveillance. MRI is usually performed without an endorectal coil.

"PI-RADS"

PI-RADS (prostate imaging reporting and data systems) communicates how likely that a spot (lesion) is prostate cancer (as opposed to inflammation or scar tissue) on a 1-to-5 scale. Lesions with a score of 4 or 5 are more likely to represent clinically significant prostate cancer (Gleason 4+3=7 or higher). Once MRI detects a suspicious lesion, a targeted biopsy can be performed.

Evaluating Undiagnosed Men with High PSA Levels

There are notable advantages of starting with an MRI rather than jumping immediately to doing a random 12-core biopsy. First, MRI is less likely to diagnose clinically harmless cancers, sparing patients from unnecessary anxiety. Second, well-performed MRI only misses significant cancer about 10 percent of the time, and these missed cancers tend to be small and unlikely to spread. To put this in perspective, a well-performed 12-core random biopsy misses high-grade cancer 20 percent of the time.

MRI for Active Surveillance

Until recently, men on active surveillance have only been monitored with periodic 12-core random biopsies and PSA testing. MRI provides three advantages over random biopsy. First, imaging is noninvasive. Second, imaging can find suspicious areas that might have been missed by previous random biopsies. Third, imaging provides a baseline measurement of the cancer's size that can be used for follow-up monitoring to detect enlargement. As logical as imaging sounds, active surveillance strategies currently performed in most academic centers do not yet routinely use MRI to detect cancer progression. Nevertheless, this concept is gaining traction.

The Future of Prostate MRI

The same imaging techniques for identifying prostate cancer for targeted biopsy can also be used to direct treatment. Focal therapy spares much of the surrounding normal prostate tissue from unnecessary damage. Given the increasing reliance on accurate imaging for state-of-the-art care, the importance of finding centers of excellence with skilled and experienced physicians will assume greater and greater importance.

CHAPTER 5

Color Doppler and Micro Ultrasound

State of the art ultrasound with Color Doppler Ultrasound (CDU) and Micro-Ultrasound (MU) are outpatient imaging modalities for prostate cancer that provide useful information about staging, tumor size and location, bladder function, and potentially, prostate inflammation (prostatitis). CDU and MU can also provide a convenient way to do outpatient targeted biopsies. CDU and MU are different from the relatively crude ultrasound devices used by urologists to perform 12-core random biopsies. These low-budget devices are rarely utilized to image the prostate itself. Rather they are only to delineate the outline of the gland so that the urologist does not miss the gland altogether when performing a random biopsy.

CHAPTER 6

Body Scans and Other Predictive Factors

While multiparametric MRI is an excellent tool for monitoring disease inside the prostate, scanning the rest of the body for cancer that may have spread to the lymph nodes or bones is also critical. Body scans are necessary for every Stage of Blue except Sky. Traditionally, doctors have relied on CT scans and bone scans. However, their accuracy is disappointing. Undetected spread is the most common reason for cancer recurrence after the initial treatment.

PSMA-PET scanning technology can be used to detect prostate cancer both inside and outside the prostate. It can be used to add clarity to MRI when staging initial treatment, and it can be used in cases where prostate cancer has spread outside of the gland. It is highly specific to prostate cancer and detects lesions with greater accuracy than any scan. These scans have transformed the management of prostate cancer and can detect disease at a much earlier stage, allowing for more precisely targeted treatments. PSMA technology can potentially change the way that men with local or advanced disease are treated and is a modern component of prostate cancer treatment.

Although PSMA-PET works for most cases of prostate cancer, a small subset of prostate cancer does not express PSMA and therefore other scans must be used. Another FDA -approved scan is FACBC (Axumin), which detects increased amino acid metabolism in the cancer cells.. Another PET scan called NaF18 (radioactive sodium fluoride) provides superior specificity and sensitivity when compared with older Technetium-99 bone scans. Unfortunately it is not usually coveredby insurance. Other more esoteric PET scans that may occasionally be considered are FDG and C11 Choline. These scans provide an alternative for men with the uncommon subtype of cancer that is invisible to PSMA-PET Scans.

This wraps up the introductory section. Armed with the results from your quiz in Chapter 1, which enables you to determine your Stage of Blue, it is now possible for you to jump ahead to the Chapter that addresses your Stage specifically:

Sky:	Chapter 7
Teal:	Chapter 15
Azure:	Chapter 25
Indigo:	Chapter 30
Royal:	Chapter 36

CHAPTER 7

Sky Overview

PSA, Gleason score and imaging studies enable us to accurately identify Sky a Low-Risk type of prostate cancer which is harmless. Sky prostate cancer grows at a snail's pace compared to other cancers. Active surveillance, close monitoring over time, is the method used to double check and confirm that these Low-Risk tumors are not misbehaving.

Fifteen years ago, surgery was called the "Gold Standard." What changed? In 2012, The New England Journal of Medicine published a study by Dr. Timothy Wilt comparing the long-term outcome of surgery with observation. Survival in both groups was identical!

The problem with surgery is most men have long-lasting negative consequences. You might not hear about these struggles because many men are embarrassed to talk about wearing a diaper or being impotent. Instead, they emphasize their gratefulness for being "free from cancer," unaware perhaps that their life was never threatened in the first place.

With active surveillance, appropriately selected men can forego immediate intervention, and in most cases, postpone destructive treatment indefinitely. The rationale for choosing active surveillance stands on the scientific validation of its safety, and the realization that sexual and urinary dysfunction from unnecessary surgery or radiation is unacceptable.

CHAPTER 8

Active Surveillance

If every eligible candidate in North America and Europe pursued active surveillance, close to 300,000 men could be spared from unnecessary surgery and radiation every year. To date, the published literature on surveillance includes numerous prospective studies. These studies, which evaluate men who were mostly Gleason 3+3=6, fail to identify any increased risk of prostate cancer mortality.

Active Surveillance Technique

The way men on surveillance are managed is evolving rapidly. Historically, after the initial diagnosis of Gleason 6, a PSA blood test is performed every three months for the first two years, and then every six months thereafter. Another random biopsy is recommended within three to twelve months after the initial diagnostic biopsy and every two to three years thereafter until the patient reaches age 80 or has a life expectancy under five years because of other serious medical issues.

Newer thinking relies less on random biopsy and more on MRI (Chapter 4) In a MRI-based protocol men undergo annual MRI at a center of excellence. Each year's newly obtained images are compared to the previous year looking for growth or change in pre-existing lesions or the development of any new lesions. If any such changes occur, targeted biopsies are obtained from the specific area of concern.

PSA Monitoring on Active Surveillance

Experience has shown that PSA cannot be relied upon to make final decisions about treatment in men on active surveillance. This represents a shift in policy from earlier practice. Until MRI became available, men on surveillance with rapidly rising PSA levels (with a doubling time under three years) were usually offered treatment. One multi-institutional surveillance registry reported that 20 percent of the men participating in the study were treated because their PSA doubling time was less than three years. Another report from a study of over 1,000 men, describes the cases of five men dying of metastatic prostate cancer, all five of whom had a PSA-doubling time under two years.

The main limitation of using the rate of PSA elevation to guide therapy is the lack of specificity. Vickers, in an overview of every large active surveillance study (each study had a minimum of 200 patients), concluded that changes in PSA had no independent predictive value. In another study, traditional PSA "triggers" (doubling time less than three years, or PSA rising at a rate of more than two points per year) occurred in 50 percent of stable untreated patients, none of whom went on to develop progressive cancer, require treatment, or die of prostate cancer. These studies show that great care needs to be exercised when interpreting the significance of a rise in PSA, so that men with moderate changes don't overreact and seek unnecessary aggressive treatment.

Active surveillance, with close monitoring and delayed intervention based on risk reclassification over time, is an appealing approach for Sky patients, and a welcome antidote for the 100,000 men in the United States diagnosed every year with Gleason grade 6, many of whom, sadly to this day, are still being encouraged to undergo surgery or radiation by their doctors.

CHAPTER 9

Focal Therapy

It is estimated that as many as a third of newly diagnosed men have only one spot of cancer in their prostate. These patients may be candidates for focal treatment. Focal therapy is defined as the destruction of a section of the prostate gland rather than treating the whole prostate. The known tumor site is treated, but the other lobe and surrounding structures are spared, improving the odds that sexual potency and urinary continence will be preserved. The most common methods utilized to administer focal therapy are high intensity focused ultrasound (HIFU), cryotherapy, electroporation, laser, radiofrequency tumor ablation and radiation.

Patient Selection for Focal Therapy

To be considered for focal therapy the patient must have unilateral prostate cancer that is clearly visible on MRI.

Three Essential Criteria for Successful Focal Treatment:

1. Imaging visibility on scanning is necessary to achieve precise cancer mapping for successful focal therapy. Without clear identification of the tumor, focal therapy will end up being a blind approach, resulting in a suboptimal outcome.
2. Unilaterality of the tumor in the prostate. Careful staging is necessary to ensure that focal therapy is appropriate. The risk of incomplete eradic-tion of cancer is likely to be small in carefully screened men.
3. A skillful practitioner. Since only a portion of the prostate is targeted, precision targeting of the cancer is paramount. Experience, clinical judg ment, and proper training are essential for obtaining consistently satisfactory results.

Assuming all three of these criteria are met, focal treatment offers the potential for excellent cancer control with a much lower risk of erectile dysfunction and practically no risk of urinary problems.

CHAPTER 10

Side Effects from Treatment, An Overview

Patients in Sky are still frequently advised to have treatment. It behooves them, therefore, to learn about treatment-related side effects. Unlike the other Stages of Blue, men in Sky have a choice—the option of postponing treatment by pursuing active surveillance. Therefore, shedding light on treatment-related side effects is just as important as talking about cure rates. Due to fears about monitoring cancer, patients should continually remind themselves that Low-Risk prostate cancer is harmless and never spreads.

Men contemplating prostate cancer treatment need to consider another defining characteristic of prostate cancer—the precarious anatomic location of the prostate deep in the lower portion of the pelvis, positioned -- within millimeters-- of the bladder, the rectum, and the nerves that control erections. Treatment to the prostate, even when administered by world-class experts, commonly damages these closely situated and sensitive structures, often permanently.

Patients tend to underestimate the potential side effects of surgery or radiation. An essential part of the educational process for men who are newly diagnosed is learning about the consequences that often arise after surgery or radiation. This is the subject of the next three chapters.

CHAPTER 11

Sexual Dysfunction

Erectile dysfunction (ED) is a risk with every type of treatment for prostate cancer, but the exact risk is very specific to each patient. The better a man's erections are before prostate cancer treatment, the better chance he has of preserving function. However, even in the hands of the finest surgeons only 15% of men will enjoy undiminished erectile function two years after the operation.

Changes in Ejaculation and Orgasm

Men will no longer ejaculate after their prostate is surgically removed. After radiation, most men will also develop dry orgasms. Changes in the sensations associated with orgasm occur at about the same frequency with radiation or surgery.

Penile Size and Shape Changes

One of the most devastating consequences of prostate cancer treatment involves the change in penile size: penile shrinkage. This involves not only a reduction in length, but also a decrease in girth. It is estimated that about 70 percent of men will observe a change in the size of the penis after surgery. On average, there is about a 1 cm loss of length.

Managing Erectile Dysfunction

First-line treatment for men who have a decrease in erectile function is oral medication with Viagra, Levitra, Cialis, and Stendra. How well this works depends on how badly the nerves were damaged from treatment. Men who do not initially respond to pills should at least try them every now and then. Sometimes, over time, the nerves can heal. Some men who, for example, did not respond well to the Viagra type medications immediately after surgery, will become responsive later. As with any pill, there are side effects and contraindications. You cannot, for example, use them if you are taking certain medications such as nitrates.

One effective approach to correct ED is to use "intracavernosal injections" (ICI). This involves using a small needle to inject medicine into the base of the penis. While this may initially be anxiety-provoking, it has proven to be very effective. There are many formulations of medications and countless dosing regimens, so it is essential that your physician be familiar with all the options. You must also have a detailed discussion with your physician—and have a plan in place in case you develop a prolonged erection, known as "priapism." While uncommon, priapism is a urologic emergency, so you must understand what to do when it occurs.

Another option for increasing erectile rigidity and longevity is a vacuum erection device (VED). This involves inserting the penis into a plastic tube, which uses negative pressure to draw blood into the penis, and then slipping a ring around the base of the penis to keep the blood from draining out. As with any other erection aid, there are benefits and risks, including discomfort caused by the ring pinching the penis, and the risk that the penis could turn "cold and blue." However, it is a relatively inexpensive approach, and it does not involve using needles or the potential side effects of the oral medications.

Erectile dysfunction can also be treated surgically. An inflatable penile prosthesis (IPP) can be inserted into the penis. The prosthesis is connected by a small tube to a fluid-filled reservoir and pump, which is placed in the abdomen and scrotum, respectively. When the patient triggers a "switch" located in the scrotum, the pump draws fluid out of the reservoir and into these balloons to produce an erection. When sex is over, a separate "deflate" button causes the pump to drain the balloons and let the fluid go back into the reservoir. Generally, men are pleased with how these prostheses perform. As is the case with any type of surgery, there are risks, including infection and mechanical failure of the pump.

Conclusion

Sexual dysfunction after a man undergoes surgery or radiation is common. Although we know that the majority of men will see some decline relative to their baseline erectile function after treatment with surgery or radiation, working with skillful healthcare providers who know how to manage erectile dysfunction is essential. Even more important is choosing an experienced surgeon or radiation therapist with a proven track record of successful treatment to improve the chances of recovering erectile function after treatment.

CHAPTER 12

Surgical Side-Effects Affecting Urination

Loss of bladder control (urinary incontinence) after surgery can be a devastating complication with a very negative impact on quality of life. Bladder control problems for the first few months following radical prostatectomy are to be expected. A biofeedback program (see below) may be helpful during this period to help restore bladder control. The problem is, that in some men, incontinence persists beyond the usual three to six-month recovery period.

Biofeedback

Biofeedback is also known as "Pelvic Floor Training." Biofeedback is a useful option for incontinence of lesser severity. The treatment involves weekly one-hour visits with a trained therapist. A special sensor is inserted into the rectum and attached to a biofeedback computer. During the session, the patient is taught to contract and strengthen the pelvic muscles. Also, an electrical signal can be sent to his pelvic muscles to strengthen them. Each week, the goal is to increase muscle strength by repetition.

Medications

When the main reason for incontinence is high bladder pressure, medications such as Enablex, Vesicare, Ditropan XL, Detrol LA, the oxytrol patch, oxybutynin 3% gel, and imipramine can relax the muscle in the bladder wall. Common side effects are dry mouth, constipation, and blurry vision. These drugs can't be used in patients with glaucoma or in men who do not empty their bladder well. Two newer medications, Myrbetriq and Gemtaza, do not cause dry mouth or constipation. However, 10 percent of men who take Myrbetriq develop increased blood pressure. Another option for controlling increased bladder pressures is Botox injections into the bladder delivered through a scope inserted in the penis. The success rate is approximately 50 percent and the beneficial effects usually last for three to six months. There is, however, a 5 percent risk of urinary retention, necessitating self-catheterization three to four times per day until the effect wears off.

Interstim Bladder Pacemaker

When the treatments described above are unsuccessful, the Interstim "bladder pacemaker" may be an alternative. The permanent Interstim device requires the surgical placement of an electrode in the lower back, next to the main nerve that controls the bladder. Separately, an internal "pacemaker" is attached to the stimulation electrode and surgically implanted. This only helps bladders that are overactive and spasmodic.

Surgical Option for Men Who Have Sphincter Damage

One option for the treatment of sphincter damage is a surgical procedure called the "male sling" (see below). Another option is the surgical placement of an artificial urinary sphincter (AUS). The AUS has three components: a cuff that surrounds and helps close the urethra, a pump placed inside the scrotum, and a pressure-regulating balloon that is placed in the lower abdomen. To urinate, the pump in the scrotum is squeezed, which opens the cuff around the urethra. After three to five minutes, it closes automatically. The risk of mechanical malfunction is 15 percent at 10 years.

Male Sling Procedure

The best candidates for the male sling are men with minor degrees of stress incontinence (using only one pad per day) and without a history of pelvic radiation. Surgical implantation takes an hour and is placed via an incision between the scrotum and rectum. A catheter is left in place for 24 hours. Approximately 30 percent of men are completely dry, 40 percent are significantly improved, and 30 percent show no improvement.

Climacturia: Ejaculation of Urine

"Climacturia" is defined as ejaculating urine during orgasm. Although the exact number of cases of climacturia after surgery for prostate cancer is unknown, the estimated incidence after surgery is about 20 percent. Treatment suggestions for climacturia have included behavior modification (urinating before sexual activity and refraining from drinking water), the use of condoms, and the use of a constriction ring at the base of the penis during intercourse. Although the results of these various treatments have not been well studied, patients should be informed that ejaculating urine is a rather common post-treatment complication of radical prostatectomy.

Stricture

"Urethral stricture," or scarring and constriction of the urethra, may occur after any invasive treatment of prostate cancer. Recent literature suggests that robotic prostatectomy is associated with much lower rates of urethral stricture than older surgical techniques, occurring in about 2 percent of men. Most strictures develop within three to six months of treatment. Stricture is also frequently associated with urinary incontinence (which commonly becomes even worse after stricture treatment).

Stricture treatment options include dilation of the stricture, incision of the stricture area, repeated self-catheterization and, in rare cases, major urethral reconstruction. The treatment of incontinence with any of the surgical options listed above should be postponed for at least three to six months to ensure that "stability" of the stricture has been achieved, confirming that further stricture recurrence has been avoided.

CHAPTER 13

Side Effects from Radiation Therapy

Radiation for prostate cancer may cause short- or long-term side effects. Even though radiation targets the cancer cells, normal body tissues near the tumor can be affected. Specifically, we are talking about the rectum, small intestine, bladder, urethra, bone marrow, and sexual organs. If these organs repair incompletely, the radiation effects may devolve into scar tissue. Most side effects from radiation resolve within 1–2 months after treatment. However, a minority of men encounter long-term problems.

Fatigue

There is one radiation-related side effect that has nothing to do with the surrounding organs—fatigue, which may begin to be noticeable after two weeks or so. The maximum level of fatigue usually occurs after about four weeks of treatment and persists until the end of the treatment. After the radiation is complete, normal energy levels typically recover in four to eight weeks. Moderate-intensity exercise—walking 30 minutes at least three days each week—substantially reduced fatigue.

Sexual Function

Patients may experience painful ejaculation due to inflammation during radiation. After radiation, patients may have a reduction of semen volume or dry orgasm. Up to 50% of patients have reported a decline in erectile function following radiation therapy. Medical treatment for ED after radiation is essentially the same as the treatment after surgery. A minority of men retain fertility after radiation. However, those desiring to preserve fertility should consider sperm banking prior to treatment.

Genitourinary System (GU)

Due to the close anatomic relationship between the prostate, the bladder, and the urinary passage (called the urethra), portions of the GU system receive high doses of radiation. Symptoms such as increased nighttime urination, bladder spasms, and urinary urgency can appear approximately three to four weeks after the start of radiation. These symptoms occur in 30 to 40 percent of patients and typically resolve within one to two months. Rarely, patients report blood in the urine and painful urination during treatment. Painful urination can often be alleviated by Ibuprofen, Naprosyn, and Flomax.

Urinary incontinence during or after radiation therapy is extremely rare. Long-term scar formation leading to narrowing of the urethra (stricture) occurs in fewer than 1 percent of the patients treated at top-flight centers. Patients with a prior history of transurethral resection of the prostate (TURP) have a higher risk of urinary stricture and urinary incontinence.

Rectum

Short-term rectal side effects are usually mild in intensity and may include increased bowel movement frequency, painful defecation, and blood in the stool. These effects occur in 5 to 10 percent of patients and usually appear during the third or fourth week of treatment, reaching maximum intensity toward the end of treatment and dissipating four to eight weeks following completion of treatment. Most patients complete a standard course of radiation without any specific treatment, although in some cases dietary modifications and anti-inflammatory rectal steroid suppositories are required.

Long-term rectal side effects are uncommon but may include chronic bowel frequency, rectal bleeding, and pain. Steroid suppositories can ease symptoms, and in cases of significant rectal bleeding a formaldehyde enema has been shown to be effective. Severe long-term rectal complications, such as loss of anal sphincter control or "fistula" (a passageway connecting the rectum and another organ such as the bladder) occur in less than one in 1,000 treated patients. A treatment called SpaceOAR or Barrigel appears to be very helpful in preventing rectal problems. These agents involve a gel that is injected between the prostate and the rectal wall to create a separation large enough that the rectal wall exposure to radiation is greatly reduced.

Small Intestine

By virtue of its anatomic location in the peritoneal cavity above the prostate, the small intestine is usually unaffected. However, when pelvic lymph nodes and seminal vesicles are targeted, there is a risk of short- and long-term radiation effects on the small intestine. Short-term effects, called "enteritis," can present as bloating, loss of appetite, nausea, colicky abdominal pain, or diarrhea. It can start after the second week of radiation and reach maximum intensity in the fourth week. Treatment is aimed at reducing the symptoms with anti-nausea and anti-diarrheal medications, as well as temporary diet modification to reduce fat and lactose content. These symptoms typically resolve within three months after the completion of treatment. Late small intestine side effects from radiation may develop after several months or years. Using modern techniques, the incidence of long-term complications is expected to be less than 5 percent.

CHAPTER 14

Summary of Sky

Why are many doctors still lukewarm about active surveillance?
Here are some thoughts:

1. The concept of watching cancer instead of treating it is uncommon in general oncology since there are only a few rare cancer types that have an established methodology for active surveillance. Adapting to this radical new way of thinking takes time.
2. Doctors are concerned about lawsuits if the cancer were to spread.
3. The world is changing rapidly. It's difficult to stay abreast of all the changes. Due to having only partial knowledge, many doctors remain unconvinced that active surveillance is truly safe.
4. Due to the short nature of a typical doctor visit, it is challenging for doctors to find enough time to teach patients all the ins and outs of why active surveillance makes sense. It's more time-friendly to offer patients what they are already expecting—treatment for their cancer.
5. Treatment pays the doctor far better than observation does.

The medical community fumbled badly in the 1960s when it labeled Gleason 6 a "cancer." We now know that Gleason 6 never metastasizes. Therefore, it fails to meet even the minimum requirement of being defined as a cancer. Despite an abundance of scientific support for active surveillance many doctors and patients are still frightened. The perceived danger from "cancer" causes patients to overlook the possibility of lifelong, irreversible side effects from treatment. The medical industry, due to time constraints and mixed motives rarely offers the emotional support patients need to adopt a go-slow approach. Patients struggle to overcome their preconceived ideas about the deadliness of cancer. In addition to all of this, family members are also frightened, and tend to insist on treatment. It's no wonder that many men are attracted to surgery. They believe that cutting out the prostate will bring them relief from all the emotional uncertainty.

The Drawbacks of Active Surveillance

The biggest concern for men contemplating active surveillance is that the initial random biopsy may have missed a higher-grade tumor. Most centers address this problem by doing random biopsies every couple of years, which are unpleasant, can cause serious infections, increase the risk of impotence, and worsen urinary symptoms. Thankfully, recent studies now show that MRI (Chapter 4) is an excellent alternative to having repeated random biopsies.

Living with Cancer

Anxiety and uncertainty about living with untreated "cancer" is certainly a problem. Some degree of anxiety, however, is inescapable. Studies show that men who had surgery or radiation also struggle with fears that the cancer may come back. Men in Sky need to guard against rushing into unnecessary treatment. Too often their treatment ends up being associated with irreversible side effects.

Now that patients with Sky have finished this Section,
they can skip ahead to Chapter 43 to complete the remainder of the book.

CHAPTER 15

Teal Overview

Teal splits into three subtypes: Low, Basic, and High-Teal. Low-Teal has only one intermediate risk factor, with all the remaining predictive factors being the same as Sky. Treatment options for Teal encompasses a wide spectrum, ranging from surveillance alone for some men in Low-Teal to multimodality therapy with seeds, IMRT and TIP in men who are in the High-Teal category. Low-Teal can be very similar to Sky. As such, men with Low-Teal should read Section II starting at Chapter 7.

Men with Basic-Teal have somewhat more extensive disease in their biopsy specimen, but less than 50 percent of their cores are cancerous. Men with High-Teal, on the other hand, have two or more intermediate-risk characteristics, a Gleason grade of 4+3=7, or Gleason 7 in more than 50% of the biopsy cores. High-Teal and even Basic-Teal can metastasize. It is prudent therefore to do additional staging with MRI and PSMA-PET scans.

CHAPTER 16

Permanent Radioactive Seed Implants

Permanent seed implantation, also known as brachytherapy, involves the insertion of small, carefully spaced, radioactive pellets into the prostate. After implantation, the seeds emit a low but continuous energy over a period of one to two months, which accrues to a large total dose of radiation inside the prostate. Seed implants are performed as an outpatient procedure, which takes about 60–90 minutes.

On average, cure rates from seed implants are superior to either surgery or IMRT. This bold claim is based on the findings of the Prostate Cancer Results Study Group, a compilation of multiple reputable studies reporting cure rates. In addition, a randomized study called the ASCENDE-RT trial was completed which arrived at the same conclusion. Here are the findings of the ASCENDE-RT trial:

Cure rate at 5 years
IMRT + hormone therapy: 84%
IMRT + hormone therapy + **seeds**: 96%

Cure rate at 9 years
IMRT + hormone therapy: 70%
IMRT + hormone therapy + **seeds**: 94%

This randomized study demonstrates a dramatic 24% improvement in cure rates in patients who received IMRT + seed implant compared to those who received IMRT without seeds. Despite these stellar results, seed utilization in the United States has been declining because of economics. All the other methods of radiation treatment pay doctors at a much higher rate. It's interesting to note that the popularity of brachytherapy is growing rapidly in many countries, where physicians are paid the same rate regardless of which treatment is selected.

CHAPTER 17

High Dose Rate Temporary Seed Implants

High dose rate brachytherapy (HDR) is done in 4 steps. The first step is placement of catheters into and around the prostate. Once the catheters are in position, the two next steps are called "simulation" and "dosimetry." Simulation involves taking either a CT scan or ultrasound image of the prostate with the catheters in place. Calculations are then made to determine the dosage of radiation. A robotic delivery device controlling a single, tiny, but potent, radioactive seed attached to the end of a fine cable is inserted into each of the hollow catheters to deliver the therapy. Each treatment takes about 15–30 minutes.

HDR in combination with intensity modulated radiation (IMRT) produces consistently better cure rates than surgery. A randomized clinical trial from England reported that HDR plus IMRT is better than IMRT alone. HDR can also be used as a standalone form of therapy. HDR monotherapy cure rates are so similar to the cure rates with HDR plus IMRT that it raises the serious question as to whether the addition of IMRT provides any additional benefit.

Side Effects

Temporary urinary side effects are expected to last 1 to 2 weeks then taper off. Prostate swelling or urinary bleeding immediately after the procedure occasionally requires a temporary urinary catheter. Urinary incontinence occurs in less than 1% of cases; stricture occurs in less than 1% of men treated in top-flight centers. The risk of sexual dysfunction is similar to other forms of radiation.

CHAPTER 18

Intensity Modulated Radiation Therapy

Intensity modulated radiation therapy (IMRT) is a specialized form of external beam radiotherapy. A device called a linear accelerator is used to administer high-energy photon beams to the prostate. IMRT is delivered in small, daily doses over a course of 7 to 9 weeks. Each treatment usually takes only a few minutes. When undergoing IMRT, it is imperative that the patient be in the exact same position for each radiation treatment, so a lot of time and attention is paid to ensuring accuracy.

Why Choose IMRT?

IMRT has a long track record and a large supporting body of evidence in scientific literature. In contrast to surgery, IMRT is non-invasive and has a much lower risk of bleeding, pain, infection, urinary leakage, and shortening of the penis. In contrast to seed implants, IMRT can treat the surrounding pelvic nodes in men who are at greater risk of pelvic node metastases. In some clinical studies IMRT has also been suggested to have lower toxicity than Stereotactic Body Radiation Therapy (SBRT) or combined external radiation and seed implants.

Is TIP Necessary for Teal Patients Receiving IMRT?

The benefit of testosterone inactivating pharmaceuticals (TIP) or androgen deprivation therapy (ADT) with radiation for Teal and Azure is a well validated treatment strategy. Clinical trials show that TIP to radiation prolongs survival and decreases the risk of prostate cancer recurrence. If TIP is recommended, most patients require only 4 to 6 months of treatment. TIP can cause its own unique spectrum of side effects, though most side effects wear off with time after TIP is discontinued. Chapter 29 discusses TIP's potential side effects and how to manage them.

CHAPTER 19

Combination Therapy

The treatment recommended depends upon which subtype of Intermediate Risk a patient's cancer falls into. For example, in patients with Favorable Intermediate-Risk prostate cancer, permanent seed implants alone are preferred (Chapters 16). On the other hand, the Unfavorable Intermediate-Risk subtype tends to behave more like High-Risk. In these men a combination of seed radiation and intensity modulated radiation therapy (IMRT) is used. There is no evidence that either type of seed implant is superior to the other in terms of cancer cure rates. When combined with seeds, IMRT is usually delivered over an approximately four to five-week period and may commence several weeks prior to or after the seed implant.

When treating with IMRT alone, studies show that adding a short course of hormone therapy improves overall survival. Although there is no data to guide us, with the high radiation doses achieved using combination therapy, the anticancer effects may be sufficient enough so that the added boost from hormone therapy may no longer be necessary. However, because combination radiation therapy does not target prostate cancer that has spread outside the prostate to the pelvic lymph nodes, a certain proportion of patients with Unfavorable Intermediate-Risk prostate cancer—those who may have microscopic and thus undetected prostate cancer cells—may still benefit by receiving a short course of hormone therapy. This is the reason to consider adding four to six months of hormone therapy in Unfavorable Intermediate-Risk prostate cancer patients receiving combination radiation therapy. Whether adding IMRT and TIP to a seed implant is still necessary for men whose PSMA Pet scan shows no metastases has not been tested in prospective trials and remains unanswered.

CHAPTER 20

Proton Beam Therapy

Proton therapy is simply a beam of protons accurately delivered to a target in a fashion identical to intensity modulated radiation therapy which uses photons (IMRT). So, just like IMRT, patients visit a specialized facility and are treated daily on an outpatient basis. A typical treatment session lasts 15 to 20 minutes with most of that time devoted to patient positioning. The treatment delivery—beam-on-time—is usually less than 60 seconds. Unlike the photon radiation used in IMRT, protons come to an abrupt stop at their target point within the body.

CHAPTER 21

Stereotactic Body Radiation Therapy

Stereotactic Body Radiation Therapy (SBRT) delivers a much larger dose of radiation per patient visit than IMRT or Proton therapy. SBRT has become an accepted form of radiotherapy and meets the National Cancer Network "standard of care" guidelines for prostate cancer. The treatment course is a little more than a week long as opposed to 9 weeks for IMRT. Five fractions of high-dose radiation are administered every other day, or sometimes on five consecutive days.

CHAPTER 22

Hormone Therapy Alone as Primary Therapy for Teal

Prostate cancer cells are dependent on testosterone for their survival, so when testosterone is removed, they shrivel and die. Radiation and surgery can't cure cancer that has already spread outside the prostate. Only hormone therapy, otherwise known as testosterone inactivating pharmaceuticals (TIP), circulates throughout the whole body attacking potential micro-metastasis in the lymph nodes or bones.

One of the advantages of TIP is how easily treatment can be monitored with PSA and scans. Normally, the PSA will decline to less than 0.1 within 8 months of starting therapy. Primary TIP, therefore, is an effective way to smoke out the rare but serious types of prostate cancer in those patients whose PSA fails to decline below 0.1. Such patients should consider a more aggressive treatment with some form of radiation.

So, what is the catch? First, TIP is not curative. Most men eventually require additional treatment. Second, TIP's side effects are substantial (Chapter 29). Despite these drawbacks, with TIP, men who need treatment but are reluctant to undergo immediate surgery or radiation can "test the water" without risking the irreversible side effects commonly associated with standard surgery or radiation.

CHAPTER 23

Robotic Assisted Radical Prostatectomy (RARP)

Surgeons often claim certain advantages over radiation and other non-surgical options:

1. Examination of the surgically removed prostate allows for accurate staging, enabling doctors to make rational decisions regarding the need for further immediate treatment right after surgery. (This argument was stronger prior to the advent of modern MRI, targeted biopsies and PSMA Pet scans).
2. Surgery provides relief of obstructive voiding symptoms from BPH by getting the prostate "out of the way of the bladder."
3. Hormone therapy with TIP will not be necessary (unless after the operation a new, unsuspected degree of cancer spread is detected).
4. The accuracy of PSA monitoring for relapse is better after surgery than after radiation and other non-surgical options.
5. Salvage therapy to the prostate fossa (for local recurrence in the fossa) is usually feasible after surgery.

RARP generally takes between one and a half to three and a half hours. Thirty to sixty additional minutes are required when the lymph nodes are removed.After the operation, men wake up with a catheter that protects the new connection between the urinary bladder and the urethra. Most men will be able to go home from the hospital the following day. The catheter is removed a week later. Most can return to work within 2 to 3 weeks.

Preventative measures improve the likelihood of recovering erectile function including regular doses of Viagra. In addition, Men who want to be proactive and for men who are having zero erections should start injection therapy. A small amount of medicine is injected with a tiny needle directly into the penis several times a week. It is analogous to diabetics giving themselves insulin. With the correct dose, a full erection will result within about 10 to 15 minutes and last about an hour. These injections keep the penis healthy while the nerves are waking up. It will also allow the patient to have intercourse.

In terms of urinary recovery, twenty-five percent of men experience immediate return of complete bladder control. Fifty percent have no need for pads by 6 weeks; 85 percent are dry by 3 months; and 90 to 98 percent by one year. Results are influenced by a patient's age, preoperative bladder control, prostate size and the nerve-sparing technique used. In the few men who do not regain urinary continence, medical therapy can sometimes be successful (See Chapter 12).

CHAPTER 24

Comparing Treatments for Teal

	FAVORABLE ASPECTS		UNFAVORABLE ASPECTS			
TYPE OF TREATMENT	CURE RATES	CONVENIENCE	DISCOMFORT OF THE PROCEDURE	TECHNICAL DIFFICULTY	SHORT TERM SIDE EFFECTS	LONG TERM SIDE EFFECTS
PERMANENT SEEDS	++++	++++	--	---	--	---
TEMPORARY SEEDS	++++	+++	---	---	--	---
IMRT	++	+++	--	--	--	---
IMRT/ SEEDS	++++	+++	---	---	--	---
PROTON	+++	+++	--	--	--	---
SBRT	+++	+++	-	-	-	---
SURGERY	+++	++	----	----	----	----
TIP	+	++	-	--	---	-

Table 1

Favorable aspects of a treatment are signaled by plus (+) signs, with a single plus being the least favorable and multiple plus signs being the most favorable. Negative problems are likewise reported with minus (-) signs with multiple minus signs being even less favorable.

Additional Issues to Consider:

- Previous operations or radiation in the pelvic area increases the risk of side effects from further radiation and surgery.
- Prostate glands over 100cc can present a problem for men considering radiation.
- Treatment intensity should be knocked down to what would be appropriate for a lower Stage of Blue—for example, Teal to Sky or Azure to Teal—in very elderly or frail men with multiple pre-existing health problems.

Permanent loss of sexual and urinary function usually has substantial emotional consequences, affecting a man's capacity for intimacy and his self-esteem. Doctors in the industry often gloss over the likelihood of impotence, implying that the risks are just about the same with every type of treatment. Studies do not support this conclusion. In a survey of patients at the University of Virginia, 785 men were questioned about their sexual and urinary function every 6 months for up to 3 years after surgery or seed implantation. Half of the men who received seed implants reported recovery of sexual function back to the same level as prior to treatment. Only one-fifth of the men who had surgery reported a similar degree of full sexual recovery. Regarding urinary control, about four-fifths of the men were "back to normal" after seeds, whereas only one-half of the men reported they were normal after surgery. Clearly, the claim that side effects are equal is wrong.

When it comes time for a man to make the final choice about what kind of treatment to select, he should create a list of all the options still under consideration. Draw a line through the "worst" option and continue to eliminate options until only one remains. The final remaining option, unattractive as it is, is probably the best way to proceed.

Now that patients with Teal have finished this Section,
they can skip ahead to Chapter 43 to complete the remainder of the book.

CHAPTER 25

Introduction to Azure

The official medical terminology used by doctors for Azure is "High-Risk." Criteria for a man to be in Azure are:

1. No previous treatment with surgery or radiation.
2. One or more of the following three risk factors:
   a. PSA above 20 (but less than 100)
   b. Gleason score above 7
   c. A clinical stage of the prostate tumor that is felt by digital rectal exam extending across the midline of the gland, stage T2b (Chapter 1).
3. Any cancer detected on a scan outside the prostate including the pelvic lymph nodes, but no cancer that has spread further beyond the pelvic lymph nodes.

Azure is divided into three subcategories—Low, Basic, and High. Low-Azure is when PSA is under 10 and only small amounts of Gleason grade 8 tumor are present in one or two biopsy cores. Men with Low-Azure need to be evaluated with MRI to confirm that the tumor is relatively small and without any evidence for extracapsular extension or seminal vesicle invasion. Treatment for Low-Azure is the same as treatment for High-Teal. Men with Low-Azure should review the Teal section of the book (Section III starting with Chapter 15).

High-Azure is indicated by a Gleason score of 9 or 10 and/or a clinical stage of T3 or more (Chapter 1). High-Azure is also signaled by a PSA over 40 or when the cancer invades the seminal vesicles, the bladder, the rectum or the pelvic lymph nodes. Basic-Azure is defined as neither Low nor High.

Understanding the Importance of Microscopic Metastasis

If micro metastases are present and untreated, cancer recurrence is almost inevitable. When there is a significant likelihood of microscopic metastases, as is certainly the case with High-Azure, systemic hormonal therapy with testosterone inactivating pharmaceuticals (TIP) improves the chance for cure. One question frequently raised by patients relates to the performance of surgery to remove potentially cancerous pelvic lymph nodes with the goal of improving cure rates. While surgical removal of the pelvic lymph nodes may be useful for detecting microscopic metastases, surgical removal is not an effective method for improving cure rates. Surgeons simply can't remove all the nodes. Therefore, radiation to the pelvic lymph nodes is more comprehensive. Treatment protocols for High-Azure that fail to incorporate a strategy for treating potential microscopic metastases result in high rates of cancer recurrence.

Throughout this section of the book and the next section on Indigo, we will be continually revisiting the question of how to deal with potential microscopic metastases. Specifically, we will discuss all the different treatment modalities—TIP, radiation to pelvic lymph nodes, or chemotherapy—and when to use them. The goal is preemptive eradication of microscopic disease at an early stage, at a point when the disease is more likely to be curable. In the following chapter, we will introduce the varied ways TIP can be utilized, depending on the Stage of Blue and the circumstances of each individual patient.

CHAPTER 26

Testosterone Inactivating Pharmaceuticals

Hormonal therapy is a mainstay for Azure, Indigo, and Royal. The testosterone inactivating pharmaceuticals (TIP) fall into three broad categories:

- Lupron-like medications work by blocking luteinizing hormone (LH) which comes from the pituitary gland. When LH levels in the blood drop, the testicles stop producing testosterone. There are two types of injectable drugs that block LH. The agonists, which are called Lupron, Eligard, Trelstar, and Zoladex. There is only one injectable drug that works as an antagonist. It is called Firmagon. There is one oral medication called Orgovyx that also works as an LH antagonist.
- Anti-androgen pills "block" testosterone activity without eliminating it from the blood stream. Anti-androgens are less potent but have fewer side effects and are occasionally substituted for Lupron-like drugs in frail or elderly men. The trade names of the FDA-approved anti-androgens are Casodex, Fluamide, and Nilutamide. Their generic names are bicalutamide, eulexin, and nilandron.
- Second generation TIP such as Zytiga, Nubeqa, Erleada and Xtandi are FDA-approved medications for men who have become resistant to the "Lupron-like" medications. These medications also improve survival in men with High-Azure. 2nd Gen TIP medications work in the cancer cell internally by blocking the synthesis or the activity of testosterone. The side effects are similar to that of the Lupron-like drugs, with some exceptions (Chapter 29).

Both the anticancer efficacy and the treatment-related side effects of TIP are increased when treatment continues for longer duration. Therefore, the duration of TIP is adjusted in accordance with each individual's specific situation.

The following list presents some roles that TIP plays in prostate cancer management:

1. Men with High-Teal who are undergoing radiation often begin TIP before starting radiation and continue for a total of four to six months of therapy.
2. Men with Low-Azure have historically been given 18 months of hormone therapy.
3. Men with Basic-Azure and High-Azure who are undergoing radiation are typically treated with TIP for 18–24 months.
4. Men with relapsed disease (Indigo) often receive intermittent TIP. This means that an initial course is continued for six to 12 months and then stopped. During the off-period, PSA levels are monitored every three months. A second cycle of TIP is initiated when the PSA rises to a prespecified level, usually between 3 to 6.
5. Men with Royal who become resistant to Lupron are usually administered 2nd Gen TIP. More recently, doctors are starting 2nd Gen TIP at the first sign of metastases.
6. TIP has a potential role for shrinking an enlarged prostate gland prior to radiation.
7. TIP is an alternative to surgery or radiation for treating men with Teal (Chapter 22).
8. TIP can be used in conjunction with surgery in men with Azure. This is controversial because older studies evaluating TIP for Teal after surgery showed no improvement in cure rates. However, those studies used only three months of TIP. Subsequent studies in Azure and Indigo using TIP for a longer duration show improved survival.

CHAPTER 27

The Azure Stage of Prostate Cancer

With Azure, the first step is to make sure no detectable metastases exist outside the pelvic lymph nodes. PSMA-PET scans are particularly useful in managing high-risk prostate cancer. These scans are highly sensitive in detecting prostate cancer cells inside or outside the prostate gland. They can potentially identify metastatic disease at an earlier stage, allowing for targeted radiation that might cure the metastasis in certain scenarios.

Since cure is a top priority with Azure, a discussion of optimal treatment is necessary. Dr. Peter Grimm compiled all the studies that report cure rates for Azure. He found that either seed implants or seed implants plus IMRT, on average, provide higher cure rates compared to IMRT alone or surgery. In addition, one large randomized trial called ASCENDE-RT reported the same conclusion. The cure rate for men treated with IMRT alone was only 63 percent, whereas 83 percent of the men who received IMRT plus a seed implant.

Why Would Seeds Work Better than Surgery?

With surgery the problem is that the bladder and rectum are only millimeters from the prostate. Incomplete cancer removal (positive margins) is therefore a frequent problem with surgery. In a study of 9,300 men undergoing surgery for Azure at Johns Hopkins, 80 percent developed recurrent cancer over the subsequent 15 years. Salvage radiation ended up being necessary to "sterilize" the residual cancer in over half the patients. To avoid undergoing both surgery and radiation, it is better to simply start with radiation and skip the surgery altogether.

Prophylactic Treatment of the Pelvic Nodes with Radiation

Basic and High–Azure are associated with a substantially greater risk of microscopic cancer (cancer invisible on scans) in the pelvic nodes. Therefore, it is logical to consider giving prophylactic radiation to the pelvic lymph nodes even when the scans appear normal. However, when the risk of cancer spreading to the nodes appears to be low, pelvic radiation should be withheld.

Testosterone Inactivating Pharmaceuticals (TIP)

After IMRT and seeds, TIP is the third leg of the Azure treatment triad. In the most famous study evaluating the benefit of TIP, the mortality rate from cancer after 10 years in the men treated with TIP was reduced to 10 percent compared to 30 percent in the men who did not receive TIP. There are many additional studies that have arrived at the same conclusion. For Basic–Azure, men should receive a combination of IMRT, seed implants and TIP. IMRT should be administered to the prostate and possibly to the pelvic nodes. Men with High–Azure should receive IMRT to the prostate and lymph nodes along with TIP for 18 months. Adding Zytiga also seems prudent considering the results of recently published trials. Whether this aggressive stance should be modified in men with PSMA Pet scans showing no nodal metastases remains an untested question.

CHAPTER 28

Unorthodox Therapies for High–Azure

Chemotherapy or Zytiga for High–Azure
In a large randomized trial called STAMPEDE, men with High–Azure showed a survival improvement when six cycles of Taxotere was added to TIP / radiation compared to men treated with TIP / radiation without Taxotere. Two additional studies, presented at the annual meeting of the American Society of Clinical Oncology in 2017, also reported a survival advantage in men with High–Azure treated with Zytiga. Since Zytiga is less toxic than Taxotere, the unanswered question is whether Zytiga should be substituted for Taxotere or given in combination with Taxotere.

Adding TIP to Surgery in Men with Azure

The average five–year cure rate for Azure using surgery alone as reported in multiple phase II studies is only 42 percent. It is logical to wonder if starting TIP right after the operation would improve cure rates, as it does with radiation. In one study published in the New England Journal of Medicine, the ten–year survival rate was 85 percent in men treated with immediate TIP after surgery, compared to only 60 percent in men whose TIP was delayed to the time of cancer progression. In another study, Tanya Dorff, reported in the Journal of Clinical Oncology that the 5–year cure rate was improved to 87 percent if TIP was added right after surgery. Also, we should mention that some medications, not normally considered as cancer therapies, have been evaluated for their potential anticancer effects. Credible studies have reported that taking aspirin, statin drugs, and Metformin may prolong survival in men with Azure.

CHAPTER 29

Reducing the Side Effects of TIP

Blocking testosterone, a hormone that induces libido, strength, endurance, emotional stability, and potency, creates all kinds of side effects. This chapter introduces methods for counteracting these problems.

Fatigue and Lassitude—Strength training to build muscles should be considered routine for men on TIP (Chapter 45).

Hot Flashes—Low-dose Effexor or Neurontin, or acupuncture can be helpful. If these are ineffective, one can consider a transdermal estrogen patch such as Vivelle Dot.

Breast Enlargement—If there is early evidence of breast growth, an estrogen-blocking pill such as Femara should be considered. Alternatively, preventative radiation to the breast area can be administered prior to starting TIP.

Erectile Atrophy—The normal pattern of nocturnal erections can often be reestablished with the regular use of Cialis or Viagra. If these fail, injection therapy should be considered (Chapter 11).

Anemia—TIP causes some degree of anemia, though generally mild. Anemia reverses when the hormone therapy is stopped. If anemia is severe, it can be corrected with medications such as Procrit and Aranesp. Iron is not beneficial for this type of anemia.

Liver Changes—Casodex, and darolutamide can occasionally cause liver abnormalities. Monitoring with a hepatic panel blood test needs to be done routinely.

Mood Swings and Depression—Low doses of an antidepressant medication such as Zoloft, Celexa, or Paxil are very effective at reversing these unpleasant feelings.

Miscellaneous Side Effects—Nilutamide can occasionally cause lung problems. Treatment needs to be stopped immediately if shortness of breath or coughing occurs. Xtandi, in rare cases, causes seizures, so men with a seizure history can't use Xtandi. Since Zytiga can lower potassium levels, potassium needs to be monitored and supplemented if necessary. Erleada has been associated with skin rashes.

Weight Gain and Heart Problems—TIP slows metabolism, so weight gain is common. While TIP may not increase the risk of heart disease directly, weight gain causes diabetes and hypertension, and both can increase the risk of heart disease. New semaglutide medications such as ozempic can be a consideration for men with weight gain.

Osteoporosis—Prevention begins with an exercise program. Supplementation with Calcium and Vitamin D is also necessary. Medications such as Xgeva, Zometa, Boniva, Actonel, and Fosamax can also be considered. However, they can have side effects. The most serious is osteonecrosis of the jaw: gum tissue recedes, leaving exposed bone, which is susceptible to recurrent infections. The risk of developing osteonecrosis is much higher when treatment is continued for longer periods or when a tooth is extracted.

Now that the patients with Azure have completed this Section, they can skip ahead to Chapter 43 to finish the remainder of the book.

CHAPTER 30

Introduction to Indigo

Indigo is prostate cancer that has relapsed after a previous attempt at curative treatment (surgery, radiation, HIFU, laser, electroporation or cryotherapy) but without detectable cancer that has advanced into areas of the body distant to the pelvic lymph nodes. Over 50,000 men relapse after treatment every year in the United States. Often the relapses are localized to the pelvis and the possibility of cure still exists. Also, some of these "relapses" are so minor it is possible to watch them and forgo immediate treatment. When the cancer spreads beyond the pelvic lymph nodes, the stage becomes Royal, not Indigo (Chapter 36). Therefore, Indigo represents residual cancer in the previously treated prostate gland, in the prostate fossa (the area where the prostate gland was located prior to surgical removal of the gland), or in the pelvic lymph nodes. Metastases detected in the pelvic bones is Royal not Indigo.

Indigo falls into three categories: Low, Basic and High

- Low Indigo is cancer confined to the prostate or the prostate fossa. This can occur when there is residual disease after surgery noted in a pathology report, such as a positive margin or seminal vesicle invasion. Low Indigo also occurs when there is residual disease after radiation or cryotherapy is detected in the prostate by imaging or biopsy.
- Basic Indigo is a rising PSA after treatment, a clear PSMA scan and a PSA doubling time greater than 9 months.
- High Indigo is a PSA doubling time 9 months or less or surgically detected or scan detected cancer in the pelvic nodes.

The traditional approach to Low-Indigo in younger men utilizes a sequential, one-treatment-at-a-time policy with salvage treatment administered to the prostate gland or prostate fossa alone. Men with High-Indigo will often be managed with a multimodality approach using extended radiation fields and supplemental TIP to improve cure rates. In men with Basic Indigo treatment can be withheld while undergoing periodic PSA testing and scanning with PSMA Pet scans. A less aggressive treatment stance may be more appropriate as men get older.

CHAPTER 31

Radiation for Indigo

Radiation is a mainstay for salvage treatment after surgery and also one of the better salvage options for relapse after previous radiation. Radiation, when it is given preventatively, while the PSA is still undetectable, is called adjuvant therapy. Adjuvant radiotherapy can be considered for men after surgery who have positive margins. In one prospective study, adjuvant radiation improved the cure rate from 41 percent to 61 percent. In another study, the 10-year survival rate was improved from 66 percent to 74 percent with adjuvant radiation.

Radiation delayed until PSA begins to rise is called salvage treatment. Salvage radiotherapy is given to patients whose PSA either fails to become undetectable after surgery, or if the PSA subsequently rises after being undetectable. Success rates with salvage radiation are improved when the PSA is lower. The effectiveness of salvage radiation may be further improved with the addition of TIP in some patients.

What about Using TIP without Radiation?

In a study evaluating the 8-year cancer-specific survival rate with TIP alone, the survival rate with TIP alone was lower (86 percent) than what was achieved with the combination of TIP plus radiation (92 percent). In a different study, the results of a retrospective evaluation of 1,338 men with node metastases, the 10-year mortality rate was reduced by as much as 40 percent in the men who received radiation and TIP compared to TIP alone.

In another study known as the EMBARK trial, researchers compared second generation TIP added to a first generation TIP to first generation TIP alone in men with biochemical recurrence. They found out that the combination of the two gave 87% five year metastasis-free survival compared to 70% five year metastasis free survival in the men given first generation TIP alone.

Radiotherapy Side Effects

A good urinary outcome is more likely if men delay radiation until full urinary recovery has been achieved after surgery. Patients who are incontinent at the time of radiation usually will remain so. Regarding erectile function, delaying radiation as long as possible improves the odds of preserving erections.

CHAPTER 32

Treatment of Indigo—Cancer Relapse

Treatment for Indigo varies per the subtype. Men with Low-Indigo are presumed to have disease confined to the prostate or where the prostate used to be located. Men with Basic-Indigo have a relatively low risk for having micro metastases in the pelvic nodes. Men with fast PSA doubling (<8mo) are at greater risk of having microscopic pelvic node metastases and are High-Indigo.

Low-Indigo is defined by: 1) clear scans, 2) a PSA doubling time over 9 months, 3) if the PSA is rising, it is less than 0.5 after surgery and less than 5.0 after radiation, and 4) the original Stage of Blue prior to initial treatment was Sky, Low-Teal, or Basic-Teal. Men in this category who relapse after radiation might consider observation. Alternatively some sort of focal salvage treatment can be considered (IMRT, SBRT, proton therapy, focal brachytherapy, cryotherapy, HIFU, electroporation or laser). Alternatively, they can consider intermittent TIP. Men with doubling times over 9 months can consider observation alone without any immediate treatment.

Basic-Indigo is defined as any one of the following, but without any proven disease in the pelvic nodes: 1) a PSA doubling time of greater than 9 months, 2) a rising PSA above 0.5 after surgery or above 5.0 after radiation, or 3) the original Stage of Blue was High-Teal or Azure. Men who had previous surgery are typically treated with IMRT to the prostate fossa and the pelvic lymph nodes along with TIP. Men who underwent previous radiation should receive TIP plus IMRT to the pelvic lymph nodes. Focal treatment with one of the focal options listed for Low-Indigo can be used for persistent disease in the prostate.

High-Indigo is characterized by unequivocal pelvic node metastases and warrants multimodality therapy with long-term TIP (with Zytiga), IMRT to the nodes and in occasional cases, Taxotere.

CHAPTER 33

Unorthodox Therapies for Indigo

Some of the unorthodox treatments for Azure discussed in Chapter 28, such as aspirin, metformin, and statins, may be worthy of consideration for Indigo. Treatment with ancillary agents such as these should generally be considered as additions rather than substitutions to an overall protocol that includes standard anticancer therapies.

Observation for Elderly Men with Low-Indigo or Basic-Indigo

Normally, observation alone is reserved for men with PSA doubling times over 9 months. However, delaying therapy in older men with shorter doubling times can also be considered because the testosterone inactivating pharmaceuticals are very powerful back up therapy and capable of salvaging progressive disease and putting it in remission for years. Even milder form of TIP, using Casodex alone, can be considered. Casodex by itself has fewer side effects than Lupron-based TIP therapy.

Taxotere for Basic-Indigo

A large, randomized clinical trial called STAMPEDE confirmed Taxotere improves survival for High-Indigo. There is also some limited evidence that Taxotere may improve cure rates for Basic-Indigo. In one prospective study of 60 patients, 25 percent of the men who began Taxotere, while the PSA was still less than 3.0, appear to have been cured using 4 cycles of Taxotere combined with 9 months of TIP. Patients often ask what we mean by "cure." After surgery, cure means that the PSA remains undetectable indefinitely in men whose testosterone levels have recovered back to normal levels. After radiation, cure means a recovered testosterone and PSA levels that remain stable under 1.0.

CHAPTER 34

Minimizing the Side Effects of Chemotherapy

The most common side effect from Taxotere or Jevtana is fatigue. If tiredness from Taxotere becomes excessive, changing the schedule of infusions to weekly may be less toxic. Also, the tiredness may be reduced by switching from Taxotere to Jevtana. Other side effects and methods to counteract them are briefly summarized here:

Low Blood Counts

If the white blood count (WBC) drops below 500, the risk of blood infections sharply increases. Neulasta and Leukine increase the WBC. When a low red count occurs, called anemia, Aranesp or Procrit can build it back up. If these are ineffective, a transfusion may be necessary. Men with low platelet counts should stop aspirin and other anticoagulants. Bleeding should be treated with a platelet transfusion.

Counteracting Fatigue

Exercise can make a significant difference (Chapter 45). Prednisone, Provigil, Nuvigil, Ritalin, caffeine, and ginseng (Chapter 46) may also improve energy levels. If fatigue is severe, the chemo dosage may need to be reduced or the time between infusions extended.

Other Side Effects

Hair loss is reversible and can be prevented with ice caps. Nausea is uncommon due to the modern anti-nausea medicines. Taxotere affects the taste buds, so keeping ice chips in the mouth during the infusion is advisable to reduce blood flow to the mouth. "Icing" of the fingertips during the infusion prevents fingernail weakening. Narrowing of the tear ducts can occur. Excess tearing may require an ophthalmology consultation to unblock the tear ducts. Another side effect of chemotherapy is neuropathy. Usually, it slowly reverses after the Taxotere is stopped.

CHAPTER 35

Situations Where PSA is Misleading

PSA is a powerful blood test for detecting a cancer relapse. However, there is always a danger of misinterpretation.

PSA Rise after Surgery

Occasionally, surgeons leave a small piece of the prostate behind after surgery. In such cases, PSA may hover indefinitely in the 0.1 to 0.3 range, even when no cancer is present. When evaluating a man with low levels of detectable PSA, the original Stage of Blue should be considered. If it was Sky, then benign prostate gland cells are a more likely explanation. In this scenario, PSA should be monitored to determine if there is an upward trend or not. Sequential scans to determine if a small nodule is present and growing may provide some additional information. PSA levels that don't rise and nodules that don't enlarge are more likely to be from persistent, noncancerous residual prostate tissue.

PSA Rise after Radiation

Noncancerous PSA elevations after radiation are common, particularly after seeds. This is called the "PSA bounce" and is thought to result from radiation-induced inflammation of the prostate gland. A cancer relapse can be distinguished from a bounce by examining sequential PSA levels. A smooth upward progression is typical of a cancer relapse. Whereas with a bounce, levels tend to oscillate up and down in a zigzag pattern. Another factor to be considered is the original Stage of Blue because relapses after Azure are more common than after Teal. Other factors that influence PSA levels after radiation are the size of the prostate gland and the testosterone level. Correctly interpreting PSA levels after radiation requires oversight by a physician experienced with the treatment of prostate cancer. Now that we have PSMA scans, distinguishing a cancer relapse from a PSA bounce is much easier.

Now that patients with Indigo have finished this Section,
they can skip ahead to Chapter 43 to complete the remainder of the book.

CHAPTER 36

Overview of Royal

Royal is defined as the presence of metastases located outside the pelvic lymph nodes or the development of resistance to one of the Lupron-like drugs. Royal is the most life threatening of all the Stages and requires aggressive treatment. The overarching goal is to use maximal treatment to achieve a complete cancer remission and reduce the PSA level to less than 0.1 and for all visible disease to disappear on PSMA PET scans.

There are two ways that patients end up in the Royal stage. One pathway begins with PSA screening leading to a cancer diagnosis of Sky, Teal or Azure followed by local treatment. After a period of time, a cancer relapse occurs, and the Stage of Blue becomes Indigo. Typically, hormonal therapy with Lupron is started. Normally, after about 10 years, resistance to Lupron develops and the Stage becomes Royal.

Royal can also occur by a different pathway in men who do not undergo PSA screening. These individuals come to medical attention when they seek an explanation for bone pain. Evaluation with diagnostic scans reveals that the cancer has already metastasized to the bone.

Three subtypes of Royal can be defined: Low, Basic and High. In Low-Royal, Lupron-resistance exists, but the scans are clear of metastatic disease. This category is becoming very uncommon since the advent of PSMA scans which almost always show metastatic disease when Lupron resistance exists. Basic-Royal occurs when five or fewer metastases are detected by a scan, with at least one of the metastases located outside or beyond the pelvic lymph nodes. High-Royal means that there are over five metastatic sites with at least one of them located outside the pelvic lymph nodes.

When men are receiving ongoing treatment for Royal, continual monitoring is needed to assess the effectiveness of the therapy. In addition to blood testing and querying patients about any changes in pain symptoms, scans of the body and bones should be performed at least every 6 months. New scan results must be compared with the results of previous scans. This improves the doctor's ability to determine if the cancer is progressing or regressing.

CHAPTER 37

Early Hormonal Resistance: Low-Royal

Low-Royal occurs when a man who is Indigo develops a rising PSA while taking a Lupron-like drug, and the restaging PET scans are clear. Despite the clear scans, Lupron-resistance is a reliable sign that the cancer growth rate is accelerating. When Low-Royal is diagnosed, it should be looked upon as an opportunity to adopt an aggressive treatment protocol and deliver multiple treatment punches before the cancer further progresses and becomes more entrenched.

The first step: Every effort should be made to find the cancer's location. Knowing the cancer's location allows treatment to be focused more effectively and insurance coverage for FDA-approved treatments will be easier to obtain. PSMA scans (Chapter 6) detect metastases at a much earlier stage than CT scans or bone scans. Some doctors treat Low-Royal with a mild type of testosterone inactivating pharmaceutical (TIP) that is called Casodex (bicalutamide). However, this may be ill advised. Treatment with other FDA-approved, life-prolonging therapies ends up being postponed. Studies show that delaying life-prolonging therapy impairs treatment results over the long term.

The second step: If body scans fail to disclose the location of the cancer, treatment with Zytiga, Erleada, Nubeqa, or Xtandi should be initiated. Well-performed randomized trials show that these effective medications will delay the development of bone metastases by several years. These oral medications are generally well tolerated, often with no side effects beyond what men normally experience with Lupron.

Unsuspecting Doctors and Patients

Doctors and patients are often unaware of the danger from postponing effective treatment in men with Low-Royal. Why? A physician's thinking may be clouded by the many previous years of successful disease control with Lupron. They assume that the longstanding quiet behavior of the cancer will continue indefinitely into the future. Men with Low-Royal are in a strange situation. They feel healthy, and their only problem is that the PSA is rising. Unfortunately, patients and doctors alike often fail to realize that a rising PSA with a low testosterone indicates that they are entering dangerous territory.

CHAPTER 38

Oligometastatic Prostate Cancer: Basic–Royal

Rapid improvements in medical technology are forcing us to rethink our traditional approach to early metastatic prostate cancer. PSMA scans are now widely available. These scans detect prostate cancer at much lower PSA levels than any other scan previously used for prostate cancer. These new scans enable the use of spot radiation administered to metastatic sites.

Historical experience with older, less accurate scan indicated that that men with early metastases probably had additional undetected microscopic metastases in other areas of the body and attempts to cure such patients by simply treating the visible metastases will fail, since the untreated microscopic cancers will eventually grow larger, leading to cancer recurrence. Countering this pessimistic view are the results of recent studies showing that aggressive treatment directed at all the visible metastases can lead to durable remissions. Studies show that durable remissions are more common if metastasis–focused treatment is combined with systemic treatment, which is active against undetected microscopic metastases. However, all these studies were performed before the advent of modern PSMA–PET technology. PSMA scans are so superior to previously available technology that it may be that in certain cases no further microscopic metastatic disease exists. In other words, some men with a limited number of PSMA – detected metastases can be cured with lesion–directed radiation alone.

CHAPTER 39

Treatments for High–Royal

Gauging The Anticancer Treatment Effects

Metastases originate from the prostate and spread to another part of the body, most commonly the lymph nodes and bones, and less often to the liver or lungs. Early metastases are usually without symptoms. When cancer becomes widespread, a "whole–body" treatment plan with systemic therapy is necessary. The backbone of treatment is hormonal therapy with testosterone inactivat–ing pharmaceuticals (TIP), also known as androgen deprivation therapy or ADT (Chapters 26 and 29). Deprived of testosterone, prostate cancer cells can't replicate and eventually die. The most important predictor of how long TIP will remain effective is determined by the degree of PSA decline after starting TIP, the PSA nadir, which is the PSA level at its lowest point. A nadir of less than 0.1 is ideal. When the nadir is above 0.1, hormone resistance and progressive disease is likely to develop quickly.

Immunotherapy

When selecting therapy, doctors should attempt to strike a balance between a treatment's potency and its side effects. If the PSA rises while on treatment, or if new lesions appear on bone or body scans, a change in therapy is necessary. Provenge's convenience and lack of toxicity make it a logical first step when men become resistant to Lupron. Provenge requires three visits, one every two weeks, at which time leukapheresis, a process akin to dialysis, is performed to filter out white blood cells (dendritic cells) from the bloodstream. The dendritic cells are then incubated and "trained" to recognize prostate cancer. Three days later, these "primed" dendritic cells are reinfused back into the patient at the doctor's office. Dendritic cells activate the killer T cells of the immune system to attack the cancer cells directly. In general, side effects are mild, though occasionally patients will have transient fever, fatigue, nausea, headache, and flu–like symptoms.

The FDA's approval of Provenge came in 2010 after a prospective, randomized trial demonstrated improved survival compared with placebo. Provenge achieved this in men with relatively advanced disease. Their average PSA was over 50. Further studies performed in men with earlier–stage disease have shown a larger survival benefit. For example, Provenge improved survival by 13 months in men whose PSA was under 22 at the time the Provenge was initiated.

Immunotherapy with Provenge is a unique technology. Unlike other types of therapy, PSA levels don't usually decline. Critics claim this is a sign that Provenge is ineffective. Such criticism is ironic, however, considering that the FDA refuses to use PSA metrics as an indicator of drug efficacy. Instead, the FDA demands proof of extended survival in prospective, placebo–controlled trials. Two such trials evaluating Provenge in this manner confirm that Provenge prolongs survival. Even so, some may wonder, "How can life be extended without PSA dropping?" One plausible explanation is that immune enhancement impedes the growth of new cancer cells without causing immediate mortality of the existing cells.

Second Generation Hormonal Agents

Additional hormonal agents can be added or substituted when Lupron becomes ineffective., The year 2011 marked the start of a "Golden Age" of prostate cancer therapeutics, when a new oral medication called abiraterone (Zytiga) was first approved by the FDA. Zytiga works by counteracting the autologous production of testosterone that commonly occurs inside cancer cells that have developed Lupron resistance. Additionally, second generation hormone agents also reduce the production of testosterone in the adrenal glands unlike first generation hormone agents.

In a landmark trial, Zytiga was compared head–to–head with placebo in TIP–resistant men who had already tried chemotherapy. The study was stopped early because Zytiga was so effective, and the researchers felt it was unethical to continue giving placebos to the trial participants.

Generally, Zytiga is well tolerated. Potential side effects are high blood pressure, low potassium, leg swelling, and liver inflammation. Therefore, during the first few months after starting treatment, regular lab monitoring is required. Another oral medication called prednisone is also used in small doses to maintain normal potassium levels in the blood.

In 2012, another landmark medication was FDA approved called enzalutamide (Xtandi). In a clinical trial evaluating Xtandi after chemotherapy, Xtandi prolonged survival compared to placebo. The most common side effects were hot flashes and fatigue. There was also a risk of seizure, though under 1 percent. In 2014, a second clinical trial evaluating Xtandi prior to chemotherapy showed an even greater improvement in survival, and delayed the need for chemotherapy by 17 months, along with other benefits.

After Xtandi's approval, two more similar medications, Nubeqa and Erleada have been approved. In making comparisons between these four medications, there doesn't seem to be a major advantage of one over the other though Erleada has been associated with a higher incidence of skin rashes.

Chemotherapy

After a patient has been treated with a second–generation hormonal agent, and if the treatment is losing its anticancer efficacy, starting treatment with Taxotere or Cabazitaxel (Jevtana) is usually considered next. Taxotere and Jevtana are chemotherapy and have characteristics that are quite similar to each other. Most of the information provided here about Taxotere is also true for Jevtana.

Taxotere has two basic roles to play. Taxotere (or Jevtana) is usually reserved for men with progressive metastatic disease after the development of Lupron resistance as well as resistance to Xtandi and Zytiga. Now, however, new studies show that Taxotere's anticancer effects can be enhanced by using it at an earlier stage, before the onset of Lupron resistance. In one important study, four months of Taxotere added to TIP improved survival by 18 months in men with metastatic, hormone–sensitive disease. Jevtana was initially FDA approved by demonstrating a survival advantage in men who had already taken Taxotere. A more recent study comparing Taxotere with Jevtana showed that Jevtana was equally effective but caused fewer side effects.

Strengthening The Bones

Two "bone–targeted" medications, Xgeva and Zometa, strengthen bone and reduce fractures. Xgeva arrests cancer growth in the bone. Neither, however, impacts survival. With these medications, a severe problem called osteonecrosis can occur. Osteonecrosis consists of a breakdown of gum tissue allowing the exposed bone to become susceptible to recurrent infections. The risk of osteonecrosis is increased when treatment is continued at higher doses and for longer periods. Dental extractions also increase the risk.

Targeted Radiation Injected Into The Bloodstream

In 2022, Pluvicto, LU-177 was FDA approved. Lu-177 technology relies on PSMA seeking antibodies to search out cancer cells throughout the body and deliver a potent dose of radiation right to the cancer's front doorstep. Clinical trials confirm that Pluvicto has substantial anti-cancer efficacy in men with High-Royal who have had previous Taxotere. The most common side effects are low blood counts and dry mouth.

In 2013, the FDA approved Xofigo, Xofigo uses alpha emitting radiation derived from Radium-223. When tested in a randomized clinical trial, Xofigo showed a survival advantage when compared with "best clinical care" which consisted of treatment with Casodex, ketoconazole and spot radiation. Xofigo consists of a simple one-minute injection given monthly for a total of six months. Potential side effects are occasional nausea, vomiting, diarrhea or low blood counts.

CHAPTER 40

Cancer Research: Striving to Live Longer and Better

Clinical trials, research trials, and studies all refer to the process that investigates the effectiveness of a new drug, type of therapy, or combination of drugs. There are 3 main phases of an investigational treatment along the road to FDA approval. **Phase I** trials are small, and all the patients receive the investigational treatment. The focus of these studies is to elucidate the maximum safe dose for administering the treatment. **Phase II** trials are a little larger and focus on determining a drug's anticancer effectiveness. **Phase III** trials are very large. The goal is to confirm the safety and efficacy of the drug in comparison to the current "gold standard" of therapy. A survival benefit—making someone live longer—is the most common requirement for FDA approval.

If a patient is interested in participating in a clinical trial, they should consult with their physician, the one most familiar with their case. In addition, there are valuable websites i.e., www.clinicaltrials.gov that provide listings of available clinical trials. I think it is important for patients to realize that clinical trials should not be reserved only when all other treatments have failed. They should be viewed as an added tool in their quiver of treatment options. Medical advances are occurring so quickly that some new medicines may only be available in a clinical trial. Additionally, clinical trials may save money by providing free access to very expensive medications. Lastly, clinical trials advance medical science. Men who participate in clinical trials are pioneers. We all need to offer thanks to every cancer patient who has taken that major step of joining a clinical trial.

CHAPTER 41

Genetic Testing to Guide Therapy

Uncontrolled cancer cell growth results from misbehaving genes. An intriguing approach to cancer therapy is to identify mutated genes which can then be targeted with specific therapies. In some cases, a treatment to counteract the damaging effects of that gene may have been developed for the treatment of some other type of cancer besides prostate cancer.

There are still many challenges to overcome in our attempts to use a genetically guided approach. However, now that we have the ready ability to identify malfunctioning genes by name. And fortunately, technology has been developed to analyze cancer DNA released into the bloodstream. These assays are now commercially available and include Guardant 360, Foundation 1 and Caris.

The fact that targeted therapy for specific mutations can be successful has been most notably validated by the discovery of PARP inhibitors, FDA-approved drugs that target the BRCA gene. Multiple studies testing PARP inhibitor medications, such as Olaparib, have shown good responses in men with this type of mutation.

CHAPTER 42

Pain Management

Pain can occur for a variety of reasons, many which may be unrelated to cancer. Therefore, the cause of the pain needs to be accurately diagnosed for optimal management. Generally, doctors should analyze the situation in this five-step process:

I. Query the Patient Specifically about Pain.

The way we perceive pain is strongly influenced by our psychological stage of mind. In a Bayer survey of 410 men with advanced prostate cancer, two-thirds were reported to be handling their pain by ignoring it! One would normally think that uncomfortable patients visiting a doctor's office would spontaneously volunteer to their doctors that something is hurting. According to the Bayer survey, this assumption is often wrong. Unless men are specifically asked about whether they have any "aches" or "discomfort," they may visit their doctor's office and never mention that they are in pain. Denial blocks access to a correct diagnosis and ultimately to finding a solution for the pain.

II. Develop an Accurate Diagnosis. Is the Pain Cancer-Related?

Cancer pain from prostate cancer is characteristically located in the bone and tends to have the characteristics of being continuous and progressive. Pain in the joints, pain that comes and goes and transient stabbing or shooting pains are not usually from cancer. While cancer can spread to the bones, it does not spread to the joints. Joint pain comes from many things including arthritis. Arthritis can simply be due to aging. It can also come from hormone therapy. Bone pain that is suspected to be coming from metastatic cancer should be confirmed by checking a scan. A diagnosis of cancer pain is confirmed when the pain that the patient describes is in the same location as reported on the scan.

III. When the Pain is Coming from Cancer

Begin by stopping the ineffective cancer treatment and start a new cancer treatment. The best quality of life and the best survival rates come by controlling the cancer (and its pain) with effective therapy. A reduction in cancer pain generally occurs soon after starting a new therapy and is a reliable sign that the therapy is working. While waiting for the anticancer medicine to kick in, which may take days to a few weeks, pain medicines can be used.

IV. Utilize a Stepwise Escalation of Pain and Other Supportive Medications.

Milder analgesics are usually initiated first. Nonnarcotic medications such as Aleve, Motrin, Advil, Tylenol, and Celebrex are effective and often underutilized. Generally, with pain medications, treatment will be much more effective if the pain is kept suppressed with continued usage of the medication. Controlling recurring pain after the medication wears off is more difficult and will require a higher dose of medication than if the pain had been kept under control by staying on a regular schedule. All the pain medications are different and have different durations of action. Talk with your doctor about what side effects might occur. Also discuss how long the medication you are taking is expected to last in your system so you will know how often you need to do repeat dosing.

If the milder analgesics are ineffective, escalating doses of a short-acting narcotic are usually the next step. Once adequate pain control is achieved, a long-acting narcotic that only requires once or twice a day dosing can be substituted. When there is an urgent need for pain relief, cortisone medications in combination with the nonnarcotic and narcotic medications are helpful. Anti-anxiety medications or antidepressants can also be beneficial.

V. Consider Radiation and Nerve Blocks.

If the pain is located in one area of the body, standard radiation to the area of pain can be very effective. If there are multiple painful areas, injected radiation, called Xofigo (see Chap 39), is another option to consider. Neuroleptic pain, due to a tumor pushing or pinching a nerve, may be controllable with a nerve block.

With good communication and proper medical management, pain can almost always be effectively controlled. Proper management relies on a diagnostic and therapeutic sequence that accurately determines the source of the pain and utilizes medications in a stepwise and escalating fashion. If these basic measures listed here are unsuccessful, consultation with a pain specialist is the logical next step.

VII. Lifestyle and General Health Issues

CHAPTER 43

General Health Issues for Men with Prostate Cancer

The post treatment surveillance policy for men who have undergone an attempt at curative surgery or radiation is to check PSA quarterly for the first two years, biannually for the next three, and annually thereafter. For radiation patients, a yearly digital rectal examination is also recommended. After treatment with TIP, some men will be left with chronically suppressed testosterone. Several studies suggest that properly supervised administration of testosterone is safe. In addition to the need for post treatment surveillance, these ongoing doctor visits offer a good opportunity to screen men for issues unrelated to prostate cancer by important for their overall general good health.

Every man age 40 and above should have an annual physical, including a skin exam, an eye exam and blood tests. Annual flu vaccines are advisable. Prevnar-13 and Pneumovax are once-in-a-lifetime vaccines recommended for patients over 65 to reduce the risk of pneumonia. The Shingrex vaccine is recommended to prevent shingles in men who have previously had chickenpox. Men over 50 should strongly consider obtaining a CT scan to check for plaque on the coronary arteries. If there is significant plaque, aspirin, cholesterol pills and an annual stress test needs to be discussed. Men who smoke, or who have quit smoking in the last 15 years, should have an annual CT of the chest. Lung cancer can only be cured if it is detected early. Men over age of 50 (or earlier with a family history) can reduce their risk of dying from colon cancer by doing a colonoscopy or a Cologuard stool test. Lastly, men over age 70, or men who have undergone previous treatment with testosterone inactivating pharmaceuticals are at risk for osteoporosis. Osteoporosis can only be detected by doing a bone density scan.

Many problems (including prostate cancer) don't cause symptoms until the condition becomes advanced. Waiting until "something hurts" is the old-fashioned way to do medical care. Modern technology is changing the game. Live longer by diagnosing problems early, before they create symptoms and get out of control.

CHAPTER 44

Whole Nutrition for Prostate Health & Recovery

Ideally, food intake should be from whole food sources (unprocessed, unadulterated, natural), with only a small percentage of food products (processed, refined, boxed, bottled, canned, packaged, and powdered). Whole foods provide your body with essential nutrients and avoid harmful additives.

There are two kinds of sugar: complex and simple. Complex sugar comes from whole grains, beans, vegetables, and fruit, and gives enduring energy. Conversely, simple sugar offers quick, fleeting energy. Blood sugar highs and lows create hormonal and chemical stress that predisposes to inflammation, mood swings, compromised immunity, strong sugar or salt cravings, and fatigue.

Our modern diets are high in animal protein, fats, and chemicalized food. Excesses of these foods also leads to inflammation, which plays a role in atherosclerosis. Excessive saturated fats and trans-fats also stimulate atherosclerosis. Of particular concern are processed meats, which are typically manufactured with sodium nitrite, a carcinogen.

Our body is designed to consume a predominantly plant-based, whole foods diet occasionally enhanced with small quantities of animal protein. Contrary to what most people believe, an adult's daily protein requirement is not very high. By consuming a variety of quality vegetable proteins, one can easily meet their daily requirements.

Before you radically leap into a global diet change, you can make incremental healthy choices by exchanging some of your customary foods for healthier options. Making healthier choices should be based on education, common sense, and self-experimentation. When you take control and do the work, you will benefit.

CHAPTER 45

Fitness and Longevity

The risk of a sedentary lifestyle is about the same as a pack-a-day smoking habit. "Sitting is the new smoking." After age 60, just through the normal aging process, men lose 1% of their muscle every year. Hormonal treatments accelerate muscle loss. Strength training to build muscle mass, therefore, promotes optimal health.

Here is a mainstream program of weight training that will help forestall muscle loss due to aging or from hormonal therapy.

The risk of a sedentary lifestyle is about the same as a pack-a-day smoking habit. "Sitting is the new smoking." After age 60, just through the normal aging process, men lose 1% of their muscle every year. Hormonal treatments accelerate muscle loss. Strength training to build muscle mass, therefore, promotes optimal health. A reasonable program that alternates two programs every other day is outlined below. You can start without any weights whatsoever. Slowly add weight as you gain strength.

PUSH DAY
Do 3 sets of 12 repetitions

- Pectorals | Raise your arms up in front of you while lying on your back. Lower your arms back down until almost touching the ground.
- Pectorals | Stand arm's length from a wall and place your hands flat on the wall at chest level. Bend your arms slowly with a straight back. Straighten out and return your body to the starting position.
- Triceps | Extend a weight behind you while leaning forward while sitting on a chair.
- Shoulders | Extend your arms straight out on each side until they are parallel to the floor. Then start to make circles with each outstretched arm.
- Deltoid | Extend your arms straight out to each side while standing until your hands are level with your shoulders. Lower both arms back to your side.
- Abdomen | Torso twists (Do 3 sets of 25 repetitions.)

PULL DAY
Do 3 sets of 12 repetitions

- Biceps | Curl the weight up in front of you while standing.
- Back muscles | Sitting, pull your shoulder blades together; hold for 5–7 seconds.
- Back muscles | While leaning forward with one hand supported by a chair or table, dangle a weight in the free arm and pull it straight up toward your chest. Then straighten your arm until it again is fully extended.
- Legs | Stand normally. Use something next to you for balance if necessary. Bend both legs, squatting down about halfway to the floor, then straighten up. Keep your knees behind your toes.
- Calves | Start flat-footed with your feet shoulder-width apart. Push up so you are standing on your toes, then release.
- Abdomen | Sit ups (Do 3 sets of 25 repetitions.)

CHAPTER 46

Supplements for Men with Prostate Cancer

When it comes to dietary supplements, less is more. Mega-doses lead to a worse outcome in patients with cancer.

Vitamins
B12 may be needed if blood tests show a deficiency. Excess B vitamins may promote heart disease and cancer growth. Researchers have not found that Vitamin C helps prevent or treat prostate cancer. For Vitamin D, Generally, recommended is 1,000 IU daily if the level is below normal. Men with prostate cancer should not take an individual Vitamin E supplement. Higher doses of Multivitamin pills may feed prostate tumors. Taking a children's multivitamin several times a week, not to exceed one pill a day, makes more sense. Folic acid in higher amounts has been associated with a higher risk of aggressive p rostate cancer in human studies.

Fish Oil (Omega-3 fatty acids)
Pills containing EPA and DHA may reduce the risk of cardiovascular events and may have anti-arthritic and anti-depressive properties. Some new research suggests it could encourage the growth of some prostate cancers.

Ginger
500–1,000 mg per day may reduce nausea during and after chemotherapy. Korean Red Ginseng, MACA, L-arginine, L-citrulline, and American Ginseng show in preliminary data to improve sexual health. Panax ginseng may help reduce fatigue in cancer patients. American ginseng from the Ginseng Board of Wisconsin is arguably the safest, least expensive, and most effective option for fatigue.

Glucosamine, Pycnogenol, SAM-e, Lycopene and Resveratrol
Show no evidence of anti-prostate cancer activity. The few studies published to date are inconclusive and controversial.

Quercetin
It has been used with some success in chronic nonbacterial prostatitis.

Saw Palmetto & Other BPH Supplements
In two major clinical trials, the most commonly used dosage was safe but did not work better than a placebo.

Selenium
Supplements may increase the risk of aggressive prostate cancer!

Tea and Tea Supplements
Most forms of tea, including black, green, herbal, and oolong are healthy and have few or no calories, so enjoy drinking them. However, please keep in mind that tea-based dietary supplements or pills (not the drink) have no solid proof from human studies that they do anything against prostate cancer. A large clinical trial of high-dose green tea supplements in patients with advanced cancer showed no real benefit.

Whey Protein or Protein Powder
Have been shown to be ineffective at building muscle.

Zinc
Zinc supplements in high dosages, 80 to 100 mg per day or more, should be avoided. Recent human research has linked higher doses of zinc from dietary supplements to abnormal immune changes, a potential reduction in the impact of bone-building drugs, abnormal changes in cholesterol blood tests, increased risk of urinary tract infections, kidney stones, prostate enlargement, and an increased risk of aggressive prostate cancer.

Conclusion
Always talk to your doctor about any pill or supplement. Use the same approach to taking a dietary supplement as you would use for starting a prescription medication.

CHAPTER 47

The Key: Knowing Your Stage of Blue

The best protection against receiving the wrong type of treatment is good knowledge of how your particular type of prostate cancer is likely to behave. It is especially important to understand which Stage and which subtype of prostate cancer you are facing. Accurate information improves self-confidence, preparing you for a discussion with your doctor about which treatment option is best for you.

Each of the Five Stages are treated very differently. Men with more life-threatening disease need more intense treatment (and should be willing to put up with greater side effects). Men with harmless types of disease need no treatment at all. The greatest danger for Sky and Teal is over-treatment. With the other Stages of Blue there is enhanced risk by delaying treatment. Knowing one's prognosis (Stage) enables men to learn whether their treatment goals should be characterized by reticence and procrastination versus aggression and urgency.

CHAPTER 48

Summary of the Five Stages

Sky (Low-Risk) is a relatively harmless condition. The biggest risk for Sky is overtreatment. Within Sky, the most favorable subtype of all (Low-Sky) is defined by all the usual Sky criteria of Gleason 3+3=6, PSA less than 10, and minimal or no palpable disease on DRE. In addition, to qualify as Low-Sky, the PSA density must be less than 0.15 (Chapter 2), there can be no more than two biopsy cores containing cancer and no single core can be more than 50 percent involved.

Men in Low–Sky have the best chance for staying on surveillance long term without requiring treatment. At the other end of the spectrum (within Sky) is High–Sky which is defined by all the usual Sky criteria but with one or more of the following: palpable disease, a PSA density over 0.15 or more than 50% of the biopsy cores containing cancer. These men are at somewhat greater risk for disease progression, the eventual need to go off active surveillance and undergo some form of treatment. Basic–Sky falls between the Low and High subtypes. As would be expected, the risk for men with Basic–Sky to require future treatment is intermediate between Low and High.

Teal (Intermediate–Risk) is a generally low–grade condition associated with excellent long–term survival, although, unlike Sky, most men undergo treatment. In addition to all the usual Teal criteria of Gleason 7, PSA from 10–20 or palpable T2b disease (Chapter 1), men with Low–Teal are only allowed to have one of these elements. In addition, the Gleason must be 3+4=7 not 4+3=7, the amount of grade 4 must be less than 25 percent and no more than two biopsy cores can contain cancer. Many men with Low–Teal can be managed like Sky, that is, with active surveillance. The criteria for Basic Teal, also known as favorable Intermediate–Risk prostate cancer, is like Low–Teal except for having a higher number of biopsy cores with cancer, i.e., between 3 and 6. High–Teal, also known as unfavorable Intermediate–Risk prostate cancer is defined by having two or more of the usual Teal criteria or more than 6 biopsy cores that contain cancer. Chapter 19 discusses the different treatment approaches one should consider for Basic and High Teal.

Azure (High–Risk) also contains three subtypes. Low–Azure is Gleason 4+4=8 with all other criteria being favorable—two or less positive biopsy cores, no biopsy core more than 50% involved with cancer, a PSA less than 10, and minimal or no palpable disease (T1c or T2a). Men with Low–Azure can consider having treatment along the lines of what is used for High–Teal (Chapter 19). High–Azure is defined by having at least one of the following: A PSA over 40, Gleason 9 or 10, more than 50 percent positive biopsy cores, or cancer that spreads overtly outside the prostate. Basic–Azure falls between the Low and High subtypes. Basic–Azure is managed aggressively with an extended duration of hormonal therapy, seeds, and IMRT, as is High–Azure. Though with High–Azure, additional therapy with Zytiga, Taxotere, or both should be considered.

Indigo (Relapsed Disease) occurs when surgery, radiation, or some form of focal therapy fail to cure the disease. Men who are Low–Indigo are judged to be at very low risk for harboring any lymph node metastases. To qualify as Low–Indigo, the PSA must be under 0.5 after previous surgery, less than 5.0 after previous radiation or focal therapy and the PSA doubling time must be over 9 months. In addition, the original Stage of Blue prior to initial therapy with surgery, radiation, or focal therapy must be Sky, Low–, or Basic–Teal.

Men with High–Indigo have metastases proven either by surgery or with scans that show unequivocal pelvic node involvement. Scans and surgical pelvic lymph node staging in men with Basic–Indigo show no overt lymph node metastases. However, various factors suggest a significant likelihood that microscopic pelvic lymph node disease is present. Such factors include higher PSA levels, a fast PSA doubling time, or an original Stage of Blue higher than Basic–Teal. See the Table in the Appendix which provides the specific thresholds. The intensity of treatment selected for Low–Indigo may be relatively mild since less aggressive therapy may be curative and further options can subsequently be implemented if necessary. Aggressive combination therapy is often used for Basic– and High–Indigo for two reasons: To enhance longevity and to reduce the likelihood of needing additional hormonal therapy down the line. Avoiding hormonal therapy substantially improves quality of life.

Royal (Hormone–Resistance or Metastases Outside the Pelvic Nodes) is what defines Royal. Low–Royal is "pure" hormone resistance without any proven metastases. Hormonal resistance is defined as a rising PSA with a testosterone level less than 50. Basic– or High–Royal means that metastases outside of the pelvic nodes are proven to exist. With Basic–Royal the total number of metastases is five or less. Men with High–Royal have more than five metastases. Clearly, the likelihood of detecting metastases is influenced by using the best available type of scan. For example, better scans using PET technology (Chapter 6) may "convert" men who were thought to be "Low–Royal" into Basic– or High–Royal.

Treatment recommendations for Royal can vary widely because doctors are struggling to digest the explosion of new knowledge. Better treatments, improved scans, and a deeper understanding of staging, genetics, and immunotherapy have all conspired to complicate and increase the controversy about how to select optimal therapy. Overall, however, we can certainly be thankful for the many new breakthroughs and the many additional discoveries that are expected soon.

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