Prostate Cancer Staging Guide

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Prostate Cancer Research Institute
www.pcri.org

Preface

"Prostate cancer" is an umbrella term covering five major categories, each requiring different treatment. The most popular staging system for *newly-diagnosed* men integrates PSA, Gleason score, and physical examination to define three of the five categories: *Low-Risk, Intermediate-Risk, and High-Risk*. The PCRI has renamed these three categories after shades of blue: *The Sky stage*, *Teal stage, and Azure stage.* The last two stages, *Indigo* and *Royal*, represent *relapsed disease* and *metastatic disease,* respectively. Each of these Five Stages of Blue represent completely different types of prostate cancer.

Once a man's Stage of Blue is determined—by answering the questions to a quiz in Chapter 1—he is directed to a section of the book with information specifically about that Stage. In addition, each of the five stages are comprised by three subtypes. Each subtype behaves in a distinct fashion and requires different treatment. Therefore, with five stages, each with three subtypes, *15 diverse types of prostate cancer can be described.*

Understanding this staging system offers multiple benefits: 1) It locates you on the prostate cancer "map" using coordinates from your medical records, thereby providing you with a place to start, 2) it keeps the learning process from being side-tracked by irrelevant information unrelated to your Stage, 3) it points you to the best treatment options for your type of prostate cancer, 4) it brings you up to speed on the way doctors think about prostate cancer, elevating the conversation you have with your doctor to a higher level, and 5) it brings you on more equal terms with your doctor, enabling you to participate in a shared decision-making process. When you know your Stage of Blue, you can discuss your treatment preferences concisely. Then, together with your doctor, you can develop an effective and personalized treatment plan.

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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. Overall, there are four broad categories of treatment available for prostate cancer: 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 treatment on 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 Xofigo.

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." When combination therapy is being considered with the goal of improving survival, the survival advantages need to be balanced against the potential for greater side effects.

Staging and Prognosis

Chapter 1: Accessing the Medical Chart to Assign a Stage of Blue

Peter Scholz

Many treatments have irreversible consequences, so it is worth doing it right the first time. It is commonly understood in medical circles that long-term survival is improved by receiving optimal treatment up front. The first treatment is your best shot at eradicating the cancer. The initial step in the selection process is to determine your Stage of Blue.

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 the 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 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 t*he Radiolo*gy 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)

Q**uestion 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

Stanley Brosman, MD

PSA plays a variety of roles, the most familiar being screening to detect prostate cancer at an early stage. 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.

Prostate Cancer Screening is Controversial

PSA screening often leads to the detection of small, essentially harmless cancers. However, 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 modified, acknowledging the possible 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. Many men run high PSA levels from a condition called BPH that is totally unrelated to cancer. BPH is *benign enlargement* of the prostate gland, a common phenomenon associated with aging. The main issue is that PSA increases as the *gland enlarges,* but this rise in PSA has *nothing* to do with cancer.

There is a specific method for determining when the PSA is elevated higher than what would be expected for an enlarged prostate. It works by determining the

prostate size in cubic centimeters(cc) using imaging (Chapters 4 and 5) and dividing the size 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 determine when the PSA is higher than what can be attributed to an enlarged prostate. The net effect, however, is the same. 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

It's reasonable to start checking PSA yearly in men over the age of 45. Men with a family history of prostate cancer or men who are African-American should start annual testing at age 40. Men over age 75 who are in good health should continue screening.

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 Surgery or Radiation

Cancer recurrence is 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 under 1.0, though exceptions certainly exist. 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, PSA that doubles in less than three months signals aggressive disease.

Determining the Response to Hormone Therapy or Chemotherapy

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 new therapies for *Royal*—Xofigo and Provenge—clearly prolong life but may show little or no impact on PSA.

Conclusion

PSA results must be interpreted in the context of each patient's overall circumstances 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

Jonathan Epstein, MD

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 in 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 aggressive, and Gleason score 9 to 10 cancers are more so. However, some 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 on biopsy.

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

The Gleason score on 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 Is Accurate?

Assigning the correct Gleason score is developed through experience and practice. It is often 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.

Concluding Thoughts

A few years ago, there was a news story about a polar bear attacking a man in Canada. Shockingly, the report said that the bystanders did nothing to help the poor man. However, upon further review it turned out that the reporter had neglected to report that the bear was only a cub, whose reach was lower than the man's knees. When facing a monstrous behemoth like cancer, the most important question to ask is "What *kind* of cancer am I dealing with?"

Chapter 4: Prostate MRI and Targeted Biopsy

Daniel Margolis, MD

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

"Multiparametric" Means Four Scans in One

There are four different imaging components to MP-MRI. The first is called "T2-weighted," which creates the clearest images and gives the most capsular detail. The second and third parameters are called diffusion-weighted imaging (DWI) and the apparent-diffusion coefficient (ADC). These provide information about the *aggressiveness* of the tumor. The fourth, called dynamic-contrast enhancement (DCE), maps the blood flow of the tumor.

"PI-RADS"

PI-RADS (prostate imaging reporting and data systems) compiles a score composed of all four parameters—T2, DWI/ADC, and DCE—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 MP-MRI detects a suspicious lesion, a *targeted* biopsy can be performed.

Evaluating Undiagnosed Men with High PSA Levels

There are notable advantages of MP-MRI over the random 12-core biopsy. First, it is less likely to diagnose *clinically harmless* cancers, sparing patients from unnecessary anxiety. Second, well-performed MP-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 25 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. MP-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 MP-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 Ultrasound and Targeted Biopsy

Duke Bahn, MD

In Chapter 4, MP-MRI technology combined with a targeted biopsy was discussed. This chapter will discuss an alternative type of imaging, called color Doppler ultrasound (CDU). Unfortunately, CDU followed by targeted biopsy is available in only a few centers around the United States. Even so, this chapter will expound the many advantages of CDU for the diagnosis and staging of prostate cancer.

Imaging with CDU utilizes two components; grey scale imaging and color Doppler evaluation of vascularity. With CDU, cancerous lesions appear as a dark spot. In addition, cancer can show increased blood vessel density, or "hypervascularity." High-resolution CDU readily identifies tumors over 5 mm in diameter. Cancers that are visible on CDU are more likely to be clinically significant (Gleason 4+3=7 or above). Hypervascularity tends to indicate tumors with a higher grade.

PSA, Gland Volume, and Diagnosis

Using an arbitrary PSA level as a trigger for doing a 12-core random biopsy casts such a broad net that over diagnosis becomes inevitable. Men's prostates vary greatly in size—so the amount of PSA they produce varies greatly. Rather than recommending a 12-core random biopsy to every man with a slightly elevated PSA, my policy is to use a relatively low PSA threshold of 2.5 as an initial trigger to recommend a CDU evaluation. However, in men with risk factors such as family history or African-American descent, I use an even more conservative PSA cut point of 2.0 to recommend a CDU. In older men who tend to have larger prostate glands, a threshold of 4.0 is reasonable.

The first step should be to measure the size of the prostate with CDU. If a patient's PSA is higher than expected for the individual's prostate size, it increases the likelihood that an underlying high-grade prostate cancer may be present (Chapter 2 explains how to calculate a normal PSA level with allowance for the prostate's size). Men whose PSA levels are in the normal range for their prostate size should not be subjected to invasive diagnostic procedures unless other suspicious findings are uncovered during the performance of the CDU.

Questions that Color Doppler Ultrasound Can Answer:

- Where is the tumor located within the gland?
- Does the tumor remain confined within the prostate?
- What is the tumor's diameter in millimeters? Does the size of the lesion detected by imaging coincide with the length of cancer reported in the targeted needle biopsy as reported by the pathologist?
- Is tumor size or vascularity on sequential scanning increasing over time for men who are on active surveillance?

Final Thoughts on Prostate Imaging

Prostate imaging dramatically reduces the need for random biopsy. If an abnormality is detected by imaging, a *targeted* biopsy provides information that is of higher quality using far fewer stabs of the needle. Imaging should *precede* random needle biopsy. When a biopsy is required, it should be targeted rather than random.

Chapter 6: Body Scans and Other Predictive Factors

Fabio Almeida, MD

While multiparametric MRI and color Doppler ultrasound are excellent tools 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.*

Positron emission tomography (PET) scans provide three-dimensional images of the whole body. The most recent and exciting discovery is that prostate cancer relies on fat as its energy source. Prostate tumors rapidly absorb *fat* when it is injected into the bloodstream, and if the fat is made radioactive by the insertion of radioactive carbon (C11), the tumors "light up" on a scanner. Lymph node metastases as small as 5-6 mm can be detected.

After lymph nodes, bone is the second most common site of metastatic spread.

Standard bone scans use a radiotracer called Technetium-99, which is unfortunately not very specific. Other changes in the bone, such as arthritis or benign lesions, can be mistaken for cancer metastasis. A PET scan called NaF18 (radioactive sodium fluoride) provides superior specificity and sensitivity when compared with Technetium-99. NaF18 PET imaging used in combination with C11 acetate PET imaging in the same patient offers the most comprehensive method currently available for detecting cancer metastases.

C11 acetate PET scanning for prostate cancer is a giant leap forward over older scanning techniques, but the C11 scan center must be located immediately adjacent to a cyclotron facility and relatively few such centers exist. Therefore, new types of scans are being explored. Preliminary studies with Ga68 PSMA provide excellent images. Another promising new agent is FACBC (Axumin), which detects increased amino acid metabolism in the cancer cells similar to how C11 exploits increased lipid metabolism. FACBC is now FDA approved and has recently become commercially available.

This wraps up the introductory section of the book. 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

The Sky Stage

Chapter 7: Sky Overview

Mark Scholz, MD

Prostate cancer grows at a snail's pace compared to other cancers. It's such a common condition, it would be illogical to assume every case is deadly. PSA, Gleason score, imaging studies, and new genetic tests enable us to accurately identify a *Low-Risk* type of prostate cancer which is harmless. Active surveillance, close monitoring over time, is the method used to double check and confirm that these *Low-Risk* tumors are not misbehaving.

Ten 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 between both groups was identical!

The problem is that most men who undergo surgery have long-lasting negative consequences. These men downplay their struggles, too embarrassed to talk about wearing a diaper or being impotent. Instead, they emphasize their gratefulness for being "free from cancer." But perhaps they are unaware that their life was never threatened. Dr. Wilt's study confirmed that men undergoing surgery experience dramatic side effects. Seventeen percent of the men who had surgery compared to six percent of the men on observation had urinary dribbling, some losing larger amounts of urine, others having no control at all, and the remainder having an indwelling catheter. 81% who had surgery compared to 44% on observation had erectile dysfunction.

With active surveillance, appropriately-selected men can forgo 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 surgery or radiation is unacceptable.

Chapter 8: Active Surveillance

Laurence Klotz, MD

If every available candidate in North America and Europe pursued active surveillance, close to 300,000 men could be spared from unnecessary surgery and radiation every year. In one observational study of men on active surveillance with Gleason 3+3=6 or low-volume Gleason 3+4=7, men were *ten times* more likely to die of causes besides prostate cancer. In this study, 452 men on active surveillance were compared with 6,485 men having surgery, 2,264 men treated with external beam radiation, and 1,680 treated with seed radiation. *There was no difference in prostate cancer mortality.* To date, the published literature on surveillance includes 13 prospective studies, encompassing about 5,000 men. These studies, evaluating men who were mostly Gleason 3+3=6, fail to identify any increased risk of prostate cancer mortality, though one drawback is that the duration of observation in many of the studies is still short.

Active Surveillance Technique

The way men on surveillance are managed is evolving. Currently, most clinicians use the following approach or a variation of it: 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. The second biopsy should target areas in the gland that are typically *under*-sampled on the initial diagnostic biopsy. If the biopsy is either negative or confirms a relatively small amount of Gleason 3+3, subsequent biopsies are performed every three to five years until the patient reaches age 80 or has a life expectancy under five years because of other maladies or serious medical issues.

Multiparametric MRI (Chapter 4) should be performed on patients whose PSA levels have changed over time in a way that suggests more aggressive disease (usually defined as a PSA-doubling time of less than three years); whose confirmatory biopsy shows substantial increase in the cancer's size; or who are upgraded to Gleason 3+4 and who still desire surveillance as a management option. Identification of a lesion by multiparametric MRI (MP-MRI) that is suspected to be high grade should lead to a *targeted* biopsy. As quality MP-MRI centers become more widely available, it is possible that MP-MRI will replace random biopsy altogether.

Over time, in men who were initially diagnosed via random biopsy, one-third of patients will be reclassified as being at higher risk for progression and offered treatment. The rate of reclassification will vary depending on the type of criteria used for selecting active surveillance in the first place. An approach that offers surveillance to all patients with Gleason 6 and PSA less than 15, for example, will include more patients with undetected high grade disease than a policy restricted to the Epstein criteria (less than or equal to two positive biopsy cores, less than 50 percent cancer in any one core, and PSA density under 0.15). However, Epstein's stringent eligibility requirements deny surveillance to many men with disease that is not life-threatening, that is, cancer that grows slowly. Experience shows that in men who are later upgraded, the majority (85 percent) will have Gleason 3+4. Many of these men who have low-volume grade 3+4=7 are still appropriate candidates to remain on active surveillance.

When Is There Too Much Grade 6 for Active Surveillance to Be Safe?

Men with *larger quantities of Gleason 6* are at higher risk of harboring higher-grade cancer that may have been missed by the random biopsy. The exact threshold of what constitutes a "large quantity" of Gleason 6 is variable. Patients with higher-volume Gleason 6 need to be evaluated with multiparametric MRI and genetic tests such as Prolaris, Oncotype DX, or Decipher to exclude the presence of higher-grade cancer.

PSA Monitoring on Active Surveillance

PSA monitoring is helpful for identifying patients at higher risk. However, changes in PSA cannot be relied upon to make final decisions about treatment. This represents a shift in policy from earlier practice. Until MP-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 selective delayed intervention based on risk reclassification over time, is an appealing approach for *Sky* patients, and a welcome antidote for the 150,000 men in North America diagnosed every year with Gleason grade 6, who until now have been encouraged to undergo surgery or radiation. Furthermore, ongoing improvements in diagnostic accuracy of MP-MRI and genetic biomarkers will reduce the need for systematic biopsies and improve the early identification of occult, higher-risk disease.

Chapter 9: Focal Cryosurgery

Duke Bahn, MD

It is estimated that as many as a third of newly-diagnosed men have only one spot of cancer. These patients may be candidates for *focal* treatment. Focal cryotherapy is defined as the destruction of a *section* of the prostate gland by freezing. 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.

Patient Selection for Focal Cryoablation

To be considered for focal cryoablation the patient must have *unilateral* prostate cancer, that is, cancer in only one lobe. In general, men with *Sky* are the preferred candidates for focal treatment, but *Teal* and even *Azure* cancers can also be considered. Focal cryotherapy may also be offered as a salvage therapy for *Indigo*.

Methods

The cryoablation procedure uses an extremely cold temperature to destroy the cancer tissue by circulating sub-zero Argon gas through cryoprobes strategically placed in the prostate. The combination of aggressive freezing at targeted locations within the prostate, while maintaining the integrity of the urethra, external sphincter, and contralateral lobe, including the neurovascular bundle, is the premise of focal cryoablation. The results of focal cryotherapy performed at other centers, as well as at ours, show long-term stable PSA levels in 75 to 85 percent of men treated in this fashion.

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 eradication 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 judgment, 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 relatively lower risk of erectile dysfunction and practically no risk of urinary problems.

Other Types of Focal Technology

There are many other technologies that may turn out to be equally effective for administering focal therapy such as High Intensity Focused Ultrasound (HIFU), Radiofrequency Tumor Ablation (RFTA), Microwave Thermal Ablation (MTA), Photodynamic Therapy (PDT), Focal Brachytherapy, or Nanotech-Laser treatment. Focal therapy, accomplished by these other methodologies, however, is a very new area of prostate cancer therapy. There is relatively little long-term experience at centers offering focal therapy. Our reliance at the Prostate Institute of America on color Doppler, an imaging technology that has existed for over 20 years, has enabled us to hone our cryotherapy skills and build up clinical experience for more than 10 years.

Chapter 10: Side Effects from Treatment, An Overview

Mark Scholz, MD

Patients in *Sky* are still frequently advised to have treatment. It behooves them, therefore, to learn about its 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 more import-*

ant than talking about cure rates. Patients must constantly remind themselves that Low-Risk prostate cancer is totally different from other types of cancer. Let me share a stark example, a colon cancer patient who relapses after surgery will live for an average of only 13 *months*. Indeed, a very terrible situation. On the other hand, a prostate cancer patient who relapses after surgery will live for an average of 13 *years*! Even the "bad" types of prostate cancer are slow.

Keeping this drastically less-aggressive behavior of in mind, let's consider another defining characteristic of prostate cancer—its precarious anatomic location deep in the lower portion of the pelvis. The prostate is positioned perilously close, within millimeters, to the bladder, the rectum, and the nerves that control erections. Treatment to the prostate *commonly* damages these closely-situated and sensitive structures, often permanently.

Trying to reverse the side effects of prostate cancer treatment is a gigantic industry. Patients often underestimate the potential side effects of surgery or radiation. They wrongly assume it will be like recovering from an appendectomy or gallbladder operation. Even the doctors who administer surgery or radiation become desensitized. Side effects are normal to them because they see them so frequently in their daily practice. In the rush to achieve a cure, it is common for concerned patients to think that side effects won't happen to them. It is very important to slow down and "count the cost" before embarking on treatment. An essential part of the educational process for men who are newly-diagnosed is learning about the potentially serious and irreversible consequences that often arise from surgery or radiation. This is the subject of the next three chapters.

Chapter 11: Sexual Dysfunction

Kelly Chiles, MD + John Mulhall, MD

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 about 15% of men will have *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, many men will also develop dry orgasms. Hormone therapy will de-

crease the volume of ejaculate. Changes in the sensations associated with orgasm occur at about the same frequency with radiation or hormone therapy as with surgery. Anorgasmia and delayed orgasm are treatable. Problems with painful orgasm will usually resolve over time.

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. Recent evidence suggests that the loss of penile length can be offset with regular use of Viagra or Cialis.

Libido Changes

One of the common causes of decreased libido is a low testosterone level. If levels are too low, discuss with your physician whether you can take testosterone.

Managing Erectile Dysfunction

There are multiple ways that men can increase their erections. 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. 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 (much smaller than anything you would have ever seen used for drawing blood, for example) to inject medicine that causes erections directly into 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 preferably have something written out to refer to if you ever develop a prolonged erection, known as "priapism." While uncommon, priapism is a urologic emergency, so you must understand what to do in case this 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, include 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 compared with medications, and it does not involve using needles or the potential side effects of the oral medications.

The final treatment for ED is surgical. The inflatable penile prosthesis (IPP) can be used in men who do not achieve satisfactory erections using any of the previously described treatments. The IPP involves surgically inserting inflatable "balloons" into the penis. These balloons are connected by a small tube to a fluid-filled reservoir and pump, located in the abdomen and scrotum, respectively. 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. Obviously, because this is the most invasive treatment for ED, it should be considered last. There are risks inherent in any surgery, including infection. Mechanical failure of the pump, with the need for further surgery, is also a risk.

Penile Rehabilitation

Penile rehabilitation (PR) entails taking a small dose of a Viagra type medication every day (usually a quarter of the maximal dose – one pill split up into four parts), and taking a maximum dose (one full pill) once a week. As yet, there is no conclusive research published to support our claims that this policy improves outcomes. Some doctors take this as evidence that PR is not worth the time or the money. In our expert opinion, however, everything a man can do to keep his penis healthy is worth doing. The most important goal is to find a healthcare provider who appreciates how critically important sexual side effects are and has the knowledge and skills to manage all forms of dysfunction.

Conclusion

Sexual dysfunction after a man is diagnosed with prostate cancer takes many forms. Although we know that the vast majority of men will see some decline relative to their baseline erectile function, we have ways to treat this. The most important goal is to find a healthcare provider who appreciates how critically important sexual side effects are and has the knowledge about preventative care and the skills to manage all forms of dysfunction, and to choose an experienced surgeon or radiation therapist with a proven track record of successful treatment.

Chapter 12: Surgical Side-Effects Affecting Urination

Gary Leach, MD

Loss of bladder control (urinary incontinence) after surgery can be a devastating complication with a very negative impact on quality of life. The good news is that, with appropriate evaluation and treatment, incontinence is usually treatable. 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. A new medication, Myrbetriq, does not cause dry mouth or constipation. However, 10 percent of men develop increased blood pressure.

Another option for controlling increased bladder pressures, when oral medications are not successful, is Botox injections into the bladder delivered through a scope inserted in the penis. The success rate is approximately 50 percent and the 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 between 20 percent and 95 percent. As a result, many men suffer from decreased libido and decreased sexual satisfaction. 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 robot-

ic 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 been achieved, confirming that further stricture recurrence has been avoided.

Summary

Recent advances in the evaluation and treatment of incontinence offer hope for men to regain their urinary control and improve their quality of life. Bladder control problems for the first few months following radical prostatectomy are to be expected. The good news is that incontinence is usually treatable.

Chapter 13:

Side Effects from Radiation Therapy

Henry Yampolsky, MD

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 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. Such symptoms are often alleviated by Ibuprofen, Naprosyn, and Flomax.

Late urinary complications requiring nonsurgical intervention have been reported in approximately 4 percent of the intensity-modulated radiation therapy (IMRT) patients and in about 16 percent of the seed implant patients. Complications requiring surgical intervention were noted in one percent of IMRT patients and two percent of the seed implant patients. 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 2 percent of the patients. Patients with a prior history of transurethral resection of the prostate (TURP) have a higher risk of urinary stricture and urinary incontinence, especially after seed implantation.

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 new treatment called SpaceOAR may be helpful. SpaceOAR is a gel 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.

The Importance of Skillful Treatment

Many of the historical problems related to radiation have been solved with modern targeting techniques. Reduction in sexual potency is the most frequent problem, and intervention for recovery has a varied record of success. Urinary issues, with increased frequency or painful urination, are the second most common problem. GI problems are the least likely to occur. However, a small minority of men who undergo radiation therapy still encounter truly serious long-term GU and GI side effects that are difficult to manage. While treatment

Chapter 14: Summary of Sky

Mark Scholz, MD

In 2012, a survey from the Mayo Clinic and Harvard was sent to 1,439 physicians. The conclusion was that even though active surveillance is widely viewed as effective, most urologists continue to recommend surgery, while most radiation oncologists recommend radiation therapy. Why are so many doctors continuing to be lukewarm about active surveillance? Here are some thoughts:

1. Never in the history of mankind has cancer been *watched* rather than treated. Adapting to this radical new way of thinking takes time. Doctors are fearful because they would face a disastrous lawsuit if the cancer was ever to spread.
2. The medical world is rapidly changing. Doctors struggle to find time to stay abreast of all the changes. Due to a lack of knowledge, many doctors remain unconvinced that active surveillance is a safe approach.
3. Due to the short nature of a typical doctor visit, it is challenging for doctors to find enough time to teach patients about why active surveillance makes sense.
4. All things being equal, doctors would prefer to give patients what they want. Patients who are newly diagnosed with cancer are naturally looking to treat their cancer.
5. Treatment pays doctors far better than observation.

The medical community fumbled badly in the 1960s when it labeled Gleason 6 a "cancer." Now we 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 unconvinced. In their frightened state, patients don't count the cost of having lifelong, irreversible side effects from treatment. The rarely receive emotional support from their doctors and without intensive reeducation, they 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 multiparametric 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 no matter what treatment approach is selected. 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.

The Teal Stage

Chapter 15: Teal Overview

Mark Scholz, MD

Teal splits into three subtypes: *Low-Teal, Basic-Teal,* and *High-Teal.* Treatment is different for each subtype. *Low-Teal* has only one intermediate risk factor, with all the remaining factors being like those of *Sky. Low-Teal* is very similar to *Sky* and treatment with active surveillance is feasible. 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. *High-Teal*, on the other hand, has two or more intermediate-risk characteristics, a Gleason grade of 4+3=7, or Gleason 7 in more than 50% of the cores. (See Appendices I and II for further information about *Teal's* subtypes.) *High-Teal* and even *Basic-Teal* can metastasize. So a staging bone scan and an MRI or CT scan of the abdomen and pelvis should be performed before starting any treatment.

Using Scientific Studies to Compare Treatment Options

Scientific studies are the main basis for evaluating a treatment's effectiveness. Unfortunately, many studies of varying quality exist and studies can be found that will support almost any point of view. This means that not all studies are equally valid. To protect yourself from being misled, learn how to assess the quality of a study. First, don't confuse yourself by considering any *nonhuman* study. Second, realize that *retrospective* database queries are untrustworthy. The best studies are *prospective*. They compare outcomes by randomly allocating patients into separate treatment groups that can be compared over time.

When *Teal* is managed appropriately, the vast majority of men will be cured. And even if a relapse occurs, most men will live out a normal life expectancy. Therefore, as consideration is given to the various treatment options, selecting a treatment with *fewer side effects* should be the priority.

Chapter 16: Permanent Radioactive Seed Implants

Peter Grimm, DO + John Blasko, MD

Permanent seed implantation, also known as brachytherapy, involves the insertion of small, carefully spaced, radioactive pellets into the prostate. After implan-

tation, the seeds emit a low but continuous energy over a period of 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 every reputable study performed that reports 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 a seed implant compared to those who received IMRT without seeds.

What is the status of seed utilization in the United States? Shockingly, there has been a dramatic *decrease* in the use of seeds between 2002 and 2010. Prostate treatment has migrated away from seed implants, not because of science, but because of economics and politics. All the other treatments 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

Jeffrey Demanes, MD

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 by itself. 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. Men with *Low-Teal, Basic-Teal* and *Sky* can have HDR alone. *Azure* or *High-Teal* patients generally receive HDR plus IMRT with or without hormone therapy.

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 may occur in 1 to 5%. The risk of sexual dysfunction is similar to other forms of radiation.

Chapter 18: Intensity Modulated Radiation Therapy

Zachary Zumsteg, MD + Howard Sandler, MD

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 the longest track record and the largest supporting body of evidence in the 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 a larger border around the prostate, which is more advantageous for *High-Teal* patients. In some clinical studies IMRT has also been suggested to have lower toxicity than Stereotactic Body Radiation Therapy (SBRT) (Chapter 21) or combined external radiation and seed implants (Chapter 19).

Is Hormone Therapy Necessary for Teal Patients Receiving IMRT?

The benefit of combining hormone therapy, also known as testosterone inactivating pharmaceuticals (TIP), with radiation for *Teal* and *Azure* is arguably the most well validated treatment strategy in all prostate cancer. Clinical trials show that the addition of 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, beginning 2 to 3 months prior to radiation. 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

Sean McBride, MD + Michael Zelefsky, MD

The treatment we recommend at Sloan Kettering is dependent upon which *subtype* of *Intermediate-Risk* a patient's cancer falls into (see Appendices I and II). For example, in patients with *Favorable Intermediate-Risk* prostate cancer who are eligible, we tend to prefer permanent seed implants alone (Chapters 16). On the other hand, the *Unfavorable Intermediate-Risk* subtype tends to behave more like *High-Risk*. In these men we recommend using a combination of seed radiation and intensity modulated radiation therapy (IMRT).

The distinction between permanent and temporary seeds (Chapter 17) lies in the rate at which radioactivity is deposited into the prostate. 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. At Sloan Kettering, our preference is to perform the seed implant prior to the IMRT. The total course of combined therapy with seeds plus IMRT is usually completed over two months.

Compared to using either type of radiotherapy by itself, there is a two-fold rationale for using them in combination: 1) delivery of a significantly higher dose of radiation to the tumor within the prostate; 2) the addition of IMRT to seed placement allows for the treatment of *microscopic* prostate cancer that may have spread through the capsule but still remains closely adjacent to the prostate. By expanding the size of the radiation field so it includes the area just outside the edge of the prostate IMRT allows for a more robust "halo" of treatment. Studies demonstrate that, when compared to IMRT alone, the combination of HDR seeds and IMRT reduces the chance of the prostate cancer's return.

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 anti-cancer 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 distant areas of the body, a certain proportion of patients with *Unfavorable Intermediate-Risk* prostate cancer—those who may have microscopic and thus undetected prostate cancer cells that have traveled to distant sites—may still benefit by receiving a short course of hormone therapy. It is for this reason that we will consider adding four to six months of hormone therapy in *Unfavorable Intermediate-Risk* prostate cancer patients receiving combination therapy. What would trigger such a recommendation in these patients? We routinely obtain a multiparametric MRI of the prostate. Should that detect a larger-sized tumor that is pushing through the prostate capsule or into the seminal vesicles we would typically recommend the addition of hormone therapy.

Ultimately, if the toxicities of combination therapy were excessive, we could not in good conscience recommend using seeds and beam radiation together if the cure rates were only marginally better. However, studies indicate that combination therapy provides a *20 percent improvement in cure rates*. It is true that the side effects of seeds and beam radiation are increased in the short term and are marginally increased in the long term. The risk of serious disruptions to urinary and bowel function, however, is equivalent to either seeds or beam alone and, more importantly, quite low. The rates of urinary incontinence (the inability to control urine flow) are dramatically less than the rates that are typical after prostatectomy.

Chapter 20: Proton Beam Therapy

Carl Rossi, MD

Proton therapy is simply using a beam of protons to deliver precision radiation therapy. In a fashion identical to intensity modulated radiation therapy (IMRT), patients 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. Photons, and thus IMRT, expose a larger volume of healthy tissue outside the target area; men who are considering IMRT might want to consider proton therapy instead.

Recent Advances

A recent development in proton treatment is the development of *intensity-modulated* technology for protons. Intensity modulated proton therapy (IMPT) permits coverage of the pelvic lymph nodes. The Scripps Proton Treatment Center, which opened in San Diego in 2014, is the first center in the United States to use IMPT.

Clinical Trials

Initial clinical data published in 1994 confirmed the safety and efficacy of proton beam therapy. A subsequent publication that looked at over 1,200 patients was published in 1997, revealing that proton beam therapy could achieve cure rates equal to radical prostatectomy with a lower rate of toxicity. Using proton therapy, greater dose-specificity and better normal tissue sparing can be achieved over the results achievable with the older proton techniques.

Chapter 21: Stereotactic Body Radiation Therapy

Michael Steinberg, MD

Stereotactic Body Radiation Therapy (SBRT) delivers a much larger dose of radiation per patient visit than IMRT. SBRT technology is relatively new. Thus, there are fewer clinical trials comparing it with other therapies. Despite this, 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 one week as opposed to 9 weeks for IMRT.

SBRT Technology

An average of five fractions of high-dose radiation are administered every other day, or sometimes on five consecutive days. The robotic system called CyberKnife is still the most commonly used form of SBRT, though there are now several different radiation platforms for the delivery of SBRT.

Cure Rates and Side Effects

Five-years after therapy, the PSA relapse-free survival rates are 95 percent for *Sky*,* 84 percent for *Teal*, and 81 percent for *Azure*. Preliminary studies indicate that cure rates are similar with or without hormone therapy. Side effects are similar to IMRT or seed implantation. Early side effects occur in the first 3 months and then dissipate. The most common early side effects are urinary issues such as increased frequency. Urinary and bowel incontinence are very rare with any form of radiotherapy. Rectal issues include occasionally loose bowel movements, more frequent movements, or occasional bleeding from pre-existing hemorrhoids. The risk of erectile dysfunction is roughly 50 percent, similar to other types of radiation. SBRT is becoming mainstream therapy due to its greater convenience and reduced cost.

**The selection of treatment for prostate cancer is changing quickly. Ten years ago Sky was considered life-threatening and 100% of men were advised to have treatment. Back then, in 2008, practically no one was managed with active surveillance. Can treatment for Sky be justified in this modern era? Some argue for it as follows: "Since a well-performed, random, 12-core needle biopsy misses higher grade disease 20-30% of the time (when the initial Gleason grade is initially as 6), treatment is still indicated, "Just to be safe."*

Chapter 22: Hormone Therapy Alone as Primary Therapy for Teal

Mark Scholz, MD

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.

Over the years, we have treated hundreds of men with newly-diagnosed disease with TIP. Twelve-year outcomes evaluating 73 men who embarked on TIP as primary therapy have been published. After treatment, 29% never needed any further therapy; 33% required periodic re-treatment with TIP to keep their PSA levels under 5, and 38% underwent delayed local therapy such as surgery, seeds, or radiation a median of 5 years after their first dose of TIP. Out of the 28 men who had delayed local therapy, only 3 developed a PSA relapse. Upon review of this data set, we found that older men tended to have longer remissions after TIP. Less durable remissions occurred with higher starting PSA levels and higher Gleason scores.

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 0.05 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 0.05. Such patients should consider a more aggressive treatment with some form of radiation.

Considering the rapid improvements occurring in the medical world, delaying radiation or surgery keeps the option open for a better type of treatment down the line. So, what is the catch? First, TIP is not curative. Most men eventually require additional treatment. Second, while TIP's side effects are manageable and reversible, they are not trivial (Chapter 29). Despite these drawbacks, with TIP, men can "test the water" without risking the irreversible side effects commonly associated with immediate surgery and radiation.

Chapter 23: Robotic Assisted Radical Prostatectomy (RARP)

Timothy Wilson, MD

Surgery has several advantages over radiation and other non-surgical options. These advantages are:

1. Examination of the surgically-removed prostate allows for accurate staging, enabling us to make rational decisions regarding the need for immediate treatment after surgery.
2. Surgery provides relief of obstructive voiding symptoms by getting the prostate out of the way of the bladder.
3. Overall side effects of surgery are no worse than those of radiation.
4. Hormone therapy with TIP will not be necessary (unless after the operation a new, unsuspected degree of cancer spread is detected).
5. The accuracy of PSA monitoring for relapse is much greater after surgery than after radiation and other non-surgical options.
6. Salvage therapy (for recurrence) is effective and safe after surgery.

State of the Art Robotic Surgery for Prostate Cancer

Robot Assisted Radical Prostatectomy was FDA-approved for prostate cancer treatment in 2001. RARP improves accuracy, reliability and reproducibility of surgery. Compared to open surgery, blood loss is less, hospitalization time is shorter, and men tend to recover bladder control and sexual function more quickly and to a better degree.

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. I recommend regular doses of Viagra. In addition, I recommend at least one dose (100 mg) of Viagra on the third day prior to surgery. There is preliminary evidence that this decreases the shock to the nerves. Six weeks after the operation, if men are getting at least partial erections, then continuing Viagra or a similar drug is probably fine. For men who want to be proactive and for men who are having zero erections, I recommend starting injection therapy. We teach our patients how to inject a small amount of medicine with a tiny needle directly into the penis. 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. This is repeated two to three times weekly at home. It keeps the penis healthy while the nerves are waking up. It will also allow the patient to have intercourse. Men under 65 who have good erections prior to surgery have

about an 85 percent chance of having erections (without injection therapy) sufficient for intercourse within a year.

Twenty-five percent of my patients 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,

Chapter 24: Comparing Treatments for Teal

Mark Scholz, MD

Many patients operate under the mistaken belief that doctors are generally similar. However, I claim that medical oncologists like myself are quite different. This is because oncologists have no innate preference for surgery over radiation. They perform neither. In my practice in Marina del Rey, I work with two additional medical oncologists—Dr. Richard Lam and Dr. Jeffrey Turner. The three of us compiled a table comparing all the different treatment approaches for *Teal* based on our perspective as medical oncologists.

The Pros and Cons of Various Treatment Options 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	+	++	-	--	---	-

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 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 preexisting health problems.

Permanent loss of sexual and urinary function has huge consequences, affecting a man's capacity for intimacy and his self-esteem. Doctors in the industry often gloss over potential side effects, 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.

Men must put in the time to research their options. When it comes time to make the final choice, 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.

The Azure Stage

Chapter 25: Introduction to Azure

Mark Scholz, MD

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. Bone scans without metastasis.
3. One or more of the following three risk factors:
   a. PSA above 20 and less than 100, or
   b. Gleason score above 7, or
   c. A clinical stage of the prostate tumor that is felt by digital rectal exam extending across the midline of the gland i.e., stage T2b (Chapter 1).
4. 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 a multiparametric MRI (MP-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* (see Appendices I and II for further explanation of subtypes).

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, other types of therapy are much more effective. Treatment protocols for *High-Azure* that fail to incorporate a strategy for treating potential microscopic metastases are associated with higher 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

Mark Scholz, MD

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 are reduced, 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 drug that works as an *antagonist*. It is called Firmagon.
- 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, Flutamide, and Nilutamide. Their generic names are bicalutamide, eulexin, and nilandron.

- Zytiga and Xtandi are FDA-approved medications for men who have become resistant to the "Lupron-like" medications. Zytiga also improves survival in men with *High-Azure*. Zytiga works in the cancer cell *internally* by blocking the synthesis of testosterone. Xtandi also works inside the cancer cell. It prevents testosterone from activating the androgen receptor that turns on cell growth. The side effects of Zytiga and Xtandi 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 by continuing the duration of treatment for a longer period. Therefore, the duration of TIP is adjusted in accordance with each individual's specific situation. The following list presents eight ways that TIP is commonly used:

1. Men with *High-Teal* who are undergoing radiation often begin TIP two months before starting radiation and continue for a total of four to six months of therapy. As noted in the previous chapter, treatment for *Low-Azure* is similar to *High-Teal*.
2. Men with *Basic-Azure* and *High-Azure* who are undergoing radiation are typically treated with TIP for 18-24 months. Treatment starts two months before radiation and continues during and after the radiation.
3. 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.
4. With occasional exceptions, men with *Royal* generally remain on TIP indefinitely.
5. Men with *Royal* who become resistant to Lupron are usually administered Xtandi or Zytiga. Treatment with Xtandi or Zytiga is continued until there is clear evidence of new metastases on a bone scan or body scan. A rising PSA by itself, without new metastatic lesions, is an insufficient rationale to stop Xtandi or Zytiga.
6. TIP has a potential role aside from its anticancer effects to shrink an enlarged prostate gland prior to a radioactive seed implant. Otherwise, some men with excessively large prostates would be *ineligible* for seed implantation.
7. TIP can be used as a primary therapy instead of surgery or radiation to treat men with Teal (Chapter 22).
8. TIP can be used *after 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

Mark Scholz, MD

With *Azure*, the first step is to make sure no *detectable* metastases exist outside the pelvic lymph nodes. Since scanning technology is far from perfect, questionable lesions are often detected by a bone scan. These can be further evaluated with an MRI focused specifically on the lesion to determine if the questionable abnormality has a cancerous cause or is due to some other benign process. If the MRI fails to resolve the uncertainty, a CT-directed needle biopsy of the lesion may be necessary. Accurate assessment of the extent of disease and the location of the cancer in the body is essential for arriving at an optimal treatment plan.

Since cure is a top priority with *Azure*, let's consider which type of treatment leads to the best results. 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. Recently, a large *randomized* trial called ASCENDE-RT came to the *same* conclusion. The cure rate for men treated with IMRT alone was only 63 percent, whereas 83 percent of the men were cured who received IMRT *plus* a seed implant. The results of the ASCENDE-RT trial confirm that seed implants give the best results for *Basic-Azure*.

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. 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 over half the time. 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 spread to the

nodes is low, pelvic radiation should be withheld. The risk of microscopic pelvic node metastases can be calculated using the following equation:
Probability of metastasis Probability of metastasis (in %) =

$$(GS-5)\times(\frac{PSA}{3}+1.5\times T)$$

GS is the Gleason score and T is the clinical stage estimated by digital rectal examination. T = 0 for stage T1c, 1 for T2a, and 2 for T2b or T2c (see Chapter 1 under the section titled: "Clinical Stage"). Dr. Mack Roach, Chief of Radiation at UCSF, recommends that only men with a risk above 15% should undergo node radiation.

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.

Chapter 28: Unorthodox Therapies for High-Azure

Mark Scholz, MD

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 plus radiation compared to men treated with TIP plus 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, a medical oncologist from USC, 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.

Additional Options for Azure

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

Mark Scholz, MD

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

Fatigue and Lassitude

Strength training to build muscles should be considered routine (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, Flutamide, Nilutamide, and Zytiga 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.

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 of these can increase the risk of heart disease.

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, these medications 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.

The Indigo Stage

Chapter 30: Introduction to Indigo

Mark Scholz, MD

Over 50,000 men relapse after surgery or radiation each year. The characteristics of *Indigo* are: previous treatment with surgery, radiation, or cryotherapy, a clear bone scan, a normal level of testosterone in the blood, and one or more of the following:

- A rising PSA due to progressing cancer.
- Residual disease after surgery noted on a pathology report, such as a positive margin or seminal vesicle invasion. Residual disease after radiation or cryotherapy detected by imaging or biopsy.
- Surgically-detected or scan-detected cancer in the pelvic lymph nodes.

Low-Indigo is the situation where microscopic lymph node metastases are *very unlikely*. *Basic-Indigo* is when *microscopic* pelvic lymph node disease is more likely. *High-Indigo* means that node metastases are *unequivocally confirmed* by surgery or scans.

The *traditional* approach to *Low-Indigo* utilizes a sequential, one-treatment-at-a-time policy. It begins with radiation administered to the prostate fossa alone. If the cancer later resurfaces, the next step has traditionally been to start testosterone inactivating pharmaceuticals (TIP). *Indigo* can be controlled for a decade or more in this manner using ongoing TIP given either intermittently or continuously.

Over the last 5 to 8 years, due to improvements in radiation technology, it has become feasible to safely extend the radiation field to cover the pelvic nodes. Therefore, men with *Basic-Indigo* or *High-Indigo* are now candidates for a multimodality approach that relies on extended radiation fields, supplemental TIP, and possibly chemotherapy to improve cure rates.

Chapter 31: Radiation for Indigo

Christopher Rose, MD

Radiation is a mainstay for salvage treatment after surgery and a salvage option for relapse after previous radiation. Radiation, when it is given *preventatively*, while the PSA is still undetectable, is called *adjuvant* therapy. *Adjuvant* radiother-

apy can be considered for men after surgery who have extracapsular extension, seminal vesicle invasion, or 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.

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 are improved by using salvage radiation 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 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.

Radiotherapy Side Effects

A good urinary outcome depends on delaying 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 it.

Chapter 32: Indigo—Cancer Relapse or Pelvic Node Disease

Mark Scholz, MD

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* are at significant risk for micro metastases in the pelvic nodes. *Unequivocal* pelvic node metastases are associated with *High-Indigo*.

Low-Indigo is defined by: 1) clear scans, 2) a PSA doubling time over 8 months, 3) the absence of any seminal vesicle invasion or extracapsular extension, 4) if the

PSA is rising, it is less than 0.5 after surgery and less than 5.0 after radiation, and 5) the original Stage of Blue prior to initial treatment was *Sky, Low-Teal,* or *Basic-Teal*. In men who relapse after surgery, the best chance for maintaining sexual function is to delay radiation or forgo it altogether. Men who relapse after radiation are typically treated with focal cryotherapy. Alternatively, they can consider salvage seed implantation or intermittent TIP. Men with doubling times over 12 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 less than 8 months, 2) seminal vesicle invasion, 3) a rising PSA above 0.5 after surgery or above 5.0 after radiation, or 4) 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 cryotherapy or salvage seeds are 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 Taxotere.

Chapter 33: Unorthodox Therapies for Indigo

Mark Scholz, MD

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 12 months. However, delaying therapy in older men with shorter doubling times can also be considered because the testosterone inactivating pharmaceuticals are very powerful and capable 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 me what I 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

Richard Lam, MD

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, 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. 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

Mark Scholz, MD

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

PSA Rise after Surgery

A small chunk of *benign* gland is sometimes left 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 occur frequently, particularly after seeds. The "PSA bounce" 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. 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. Other factors that influence PSA levels after radiation and are the size of the prostate gland and the testosterone level. Clearly, interpreting PSA levels after radiation requires oversight by a physician experienced with the treatment of prostate cancer.

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

The Royal Stage

Chapter 36: Overview of Royal

Mark Scholz, MD

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 goal is to use maximal treatment to achieve a complete cancer remission and reduce the PSA level to less than 0.1.

There are two pathways to *Royal*. One begins with PSA screening leading to the initial diagnosis of localized disease followed by local treatment. After a period, a relapse occurs, the Stage of Blue becomes *Indigo* and 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 forgo 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. Basic-Royal occurs when there are five or fewer metastases are detected by a scan, with at least one of the metastasis 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. The optimal method for interpreting the results of new scan is to compare it 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

Mark Scholz, MD

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

Every effort should be made to find the cancer's location. When the cancer is located, treatment can be focused more effectively and insurance coverage for FDA-approved treatments is easier to obtain. Modern PET scans (Chapter 6) often detect metastases at a much earlier stage than standard CT scans or bone scans. Many doctors treat *Low-Royal* with a mild type of testosterone inactivating pharmaceutical (TIP) that is called Casodex. However, this may be ill advised because treatment with other FDA-approved, life-prolonging therapies may be postponed.

In February 2018, the FDA approved Erleada for men with *Low-Royal*. Erleada is a powerful type of TIP. Men who have clear scans, a rising PSA, and low testosterone should begin treatment with Erleada immediately. Studies show that Erleada delays the onset of metastatic disease by over two years.

Unsuspecting Doctors and Patients

Doctors and patients are often unaware that postponing effective treatment is dangerous. 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. Men with *Low-Royal* are in a strange pseudo-reality. They feel healthy, and their only problem is that their PSA is rising. However, it is the calm before the storm. Unfortunately, patients and doctors alike often fail to realize that a rising PSA with a low testosterone indicates that the patient is entering very dangerous territory. Lupron resistance is a characteristic of aggressive disease and treatment with Erleada should begin immediately.

Chapter 38: Oligometastatic Prostate Cancer: Basic-Royal

Jeffrey Turner, MD

Rapid improvements in medical technology are forcing us to rethink our traditional approach to early metastatic prostate cancer. The scans are improved; the therapies are more effective and have fewer side effects, and our understanding of how cancer spreads has been greatly enhanced. Modern theory concedes that men with early metastases *may* have additional undetected microscopic metastases in other areas of the body. 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 the undetected microscopic metastases.

An aggressive, combination approach using radiation and TIP seems to give the best results. Studies indicate that Taxotere also enhances survival in men with early metastatic disease. Practically speaking, how can all these different treatments be combined? A possible protocol for *Basic-Royal* is: 1) Start TIP with Lupron and Zytiga and continue it for a total of 12 months, 2) Taxotere is started immediately and given for a total of 4 to 6 treatments each administered 3-weeks apart, 3) Radiation is administered to the known sites of metastatic disease and possibly to the surrounding lymph-node chain starting a month after the last dose of Taxotere.

Using an aggressive protocol for *Basic-Royal* is rapidly gaining adherents. However, this approach is new and many physicians are holding back. Perhaps they are unaware of the studies or maybe they are unconvinced, considering the studies are relatively small.

Chapter 39: Treatments for High-Royal

Richard Lam, MD

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 inactivating pharmaceuticals (TIP), also known as androgen deprivation therapy or ADT (Chapters 26 and 29). Deprived of testosterone, prostate cancer cells are unable to 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 when it arrives 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.

When selecting therapy, doctors strike a balance between a treatment's potency and its side effects. If the PSA rises, or 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 sort of like 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 flulike 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 in earlier-stage disease have shown a larger survival benefit. For example, Provenge improved survival by 13 months in men with a PSA levels under 22.

Immunotherapy with Provenge is a completely new realm of therapeutic 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 changes as an indicator of a drug's efficacy. Instead, the FDA demands proof of *extended survival* in prospective, placebo-controlled trials. Two such trials 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.

Additional hormonal agents can be added or substituted when Lupron becomes ineffective. For a seasoned prostate cancer road warrior like myself, 2011 marked the start of the "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 occur *inside* cancer cells that have developed Lupron resistance.

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. In addition to extending life, Zytiga decreased PSA and improved quality of life. Subsequently, in a second study, Zytiga was again compared to placebo, but in patients with earlier stage disease. Zytiga's anticancer benefits were even more substantial.

Generally, Zytiga is extremely well tolerated. The most common side effects, if any, are high blood pressure, low potassium, leg swelling, and liver inflammation. Therefore, during the first few months of 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. Rarely, prednisone can increase blood sugar, so diabetics need monitoring of their glucose.

In 2012, another landmark event occurred. The FDA approved another highly-effective oral medication called enzalutamide (Xtandi). In a clinical trial evaluating Xtandi after chemotherapy, Xtandi prolonged survival as well as delaying the onset of pain, bone cancer progression and PSA progression. In addition, quality of life was improved. 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. In this study, there was no increase in the incidence of seizures.

In making comparisons between Zytiga and Xtandi, there doesn't seem to be a major advantage of one over the other. Each patient should compare the pros and cons. With Zytiga, the requirement for an additional drug (prednisone) to be prescribed is a disadvantage. Zytiga also requires blood monitoring to check for potassium or liver problems, whereas Xtandi does not. On the other hand, Xtandi is associated with a small risk of seizures. It can also cause fatigue more frequently.

In 2013, the FDA approved a totally new anticancer technology called Xofigo, a type of "smart radiation" that targets bone metastases. Previous attempts to achieve bone targeted radiation were ineffective and toxic. Xofigo uses *alpha emitting* radiation derived from Radium-223. Alpha radiation is much more effective and causes far fewer side effects than older radionucleotides which utilized beta radiation. 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. Although Xofigo extends survival, PSA levels often continue to rise. This "disconnect" between PSA and survival can be disconcerting to doctors and patients alike. Experts hypothesize that Xofigo's survival benefits work by *slowing the rate* of cancer cell growth rather than causing precipitous cell death.

After a patient has been treated with Provenge and Xofigo, and if Xtandi and Zytiga stop working, 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.

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.

Chapter 40: Cancer Research: Striving to Live Longer and Better

Luke Nordquist, MD

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 100 percent of the patients receive the investigational treatment. The focus of these studies is to determine a safe and effective dose of 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 a participating in a clinical trial, I recommend they start with the physician who is most familiar with their case. A second opinion from an expert is a logical next step. In addition, there are valuable websites i.e., www.clinicaltrials.gov that provide listings of available clinical trials. When embarking on a clinical trial, after an initial screening process, patients are assigned to a treatment. Typically, a clinical trial comparing two or more treatments will be randomized by a computer.

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 the bag of treatment options. Medical advances are occurring so quickly that new medicines may only be available in a clinical trial. Additionally, clinical trials may save money by providing access to expensive medications free of charge. 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

Mark Scholz, MD

Uncontrolled cancer cell growth results from misbehaving genes. An intriguing approach to cancer therapy is to specifically identify the mutated genes. After identification, 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 genetically-guided approach. While we now have the ready ability to *identify* malfunctioning genes by name, we don't always know the gene's actual function. Also, in most cases, medicines to counteract the mutations we detect don't yet exist. Another problem has been problems obtaining cancer tissue for analysis. Until recently, due to the bone-centric nature of prostate cancer metastases, *bone biopsy* was the only way to obtain access the tumor cells so genetic analysis could be performed. Fortunately, the ability to analyze cancer DNA *released into the blood stream* from dying cancer cells may now replace the need for bone biopsy. One assay, performed by Guardant Health called Guardant 360, tests for approximately 70 of the most commonly seen mutations seen in various cancers.

The fact that targeted therapy for specific mutations can be successful was most notably validated by the discovery that Olaparib, an FDA-approved drug for ovarian cancer, may also be beneficial in men with prostate cancer who have a specific mutation in the BRCA gene. It turns out that this BRCA mutation (or other related types of mutation related to DNA repair) occur fairly frequently in men with advanced metastatic prostate cancer. A study testing Olaparib for treatment of prostate cancer patients was published in the *New England Journal of Medicine*. It showed that Olaparib was very effective in 15 out of 16 men who had this type of mutation in their cancer cells. In men without this specific type

Chapter 42: Pain Management

Mark Scholz, MD

Pain can occur for a variety of reasons, many of which may be unrelated to cancer. Therefore, the *cause* of the pain needs to be accurately diagnosed to ensure that optimal treatment is selected. Generally, the situation should be analyzed with a 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 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 is does not spread to the joints. Joint pain comes from many things including the 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 bone 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. If the Pain is Coming from Cancer, First Start a New Cancer Treatment.

The best quality of life and the best survival rate comes 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 are 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 continues 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 in one area, a beam of radiation can be very effective. If there are multiple painful areas, injected radiation, called Xofigo, 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.

Lifestyle and General Health Issues

Chapter 43: Health Issues for Men with Prostate Cancer

Jeffrey Turner, MD

The surveillance policy, after 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 an 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 Zostavax 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 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 dramatically 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

Verne Varona

Ideally, the bulk of human 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.

The modern diet is 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

Mark Scholz, MD

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 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

Mark Moyad, MD

When it comes to dietary supplements, *less is more*. Mega-doses suggest a *worse* outcome or prognosis 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**, I generally recommend 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** and **Zinc** in higher amounts *have been associated with a higher risk of aggressive prostate 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. Preliminary data shows they 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

This can be taken as a powdered drink supplement (never as a pill) for any man needing more high-quality protein for health, weight loss and to support muscle health.

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.

Marijuana Cures Everything, Dude?!

So, let's review: Personally, if you are healthy, I think the risks of marijuana outweigh the benefits, unless of course you win the lottery and just want to try it one time to celebrate the fact that you never again have to listen to your boss or some of your annoying coworkers. Marijuana has NOT been proven to be heart-healthy and in fact it could be heart-*un*healthy. And the smoke does not make the lung tissue happy, even though you could feel temporarily happy.

I frequently hear, "Marijuana is natural." So, should I get excited about it? Just because it is natural is not the reason I get excited about diddly squat (aka anything). I mean, poison ivy and arsenic are natural, folks, but I usually do not recommend those things—except to my big brother when he pushed my face in the snow when we were kids...

Do I think it's possible that marijuana or one of its compounds can fight cancer or encourage the growth of cancer? Yes! But at this point, we have no conclusive evidence one way or the other. It's dangerous to treat humans unless studies *in humans* show that it works. In Europe, a laboratory study showed that a certain drug could impact a cannabinoid receptor in the brain. "Experts" were convinced that it would be a great weight-loss drug and it was marketed briefly under the trade name of Acomplia (Google that bad boy). It was removed from the market because of serious side effects such as anxiety, suicidal ideation, nausea, and, in some cases, the development of multiple sclerosis.

Final Thoughts

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

Mark Scholz, MD

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.

Knowing your Stage of Blue protects you from being assigned to the wrong treatment. As this book has clearly shown, 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. To put this into context, let's summarize the impact of the Stages of Blue on longevity:

- *Sky*—Even with no immediate treatment, shortened longevity is not a risk.
- *Teal*—Even with relatively mild treatment, shortened longevity is a very small risk.
- *Azure*—Even with combination treatment, shortened longevity is a possibility.
- *Indigo*—Even with combination therapy, there is a substantial risk of shortened longevity.
- *Royal*—Even with maximal therapy, shortened longevity occurs in over half of the men.

The greatest danger for *Sky* and *Teal* is over-treatment. With the other Stages of Blue, their risk is increased by delaying treatment. Knowing their prognosis enables men to learn whether their treatment goals should be characterized by reticence and procrastination versus aggression and urgency.

We have presented the *Five Stages of Blue*, each with 3 subtypes. Hopefully this approach is helpful. The PCRI exists to help your endeavors for an optimal outcome. Please visit our website at pcri.org or call our Helpline at (800) 641-7274 for further assistance.

Appendices

Stage of Blue	Prior Local Rx.	Gleason Score	PSA	# Biopsy Cores with Cancer	Clinical Stage	MP-MRI or CDU Scans	CT & Bone Scan	Other
Sky								
	No	3+3=6	<10		T1c	No **SVI**, Gross **ECE** or Increase in lesion Size over time	Not Needed	PSA Density
Low				1 or 2				< .15
Basic				3 to 6				
High				>6	T2a			> .15
Teal								
	No	7				*Low-Teal* = **Small** Lesion	Clear	*Low-Teal* the % of Gleason 4 in the biopsy cores must be <20%
Low		3+4=7	<10	1 or 2	T1c / T2a			
Basic			<10	3 to 6		No **SVI**, Invasion or Gross **ECE**		
High		4+3=7	10-20	>6	T1c / T2a / T2b			
Azure								
	No	8 to 10				*Low-Azure* = **Small** Lesion	Clear	*Low-Azure:* The % of cancer in the biopsy cores must be <50%
Low		4+4=8	<10	1 or 2	T1c / T2a			
Basic		4+4=8	10-40	3 to 6	T1c / T2a / T2b	*Basic Azure* = No **SVI**, Invasion, or Gross **ECE**		
High		9 or 10	>40	<6	T3a / T3b / T4 / N1			
Indigo								
	Yes		PSA and **PSADT** after Surgery/Radiation				Bone, **CT** & **PET** scans clear	Prior Stage
Low		3+4 or Less	Surgery < 0.5 / Radiation < 5 **PSADT** >8 months			No **SVI**/ **ECE**		Less than *High-Teal*
Basic		Any	Surgery > 0.5 / Radiation > 5 **PSADT** < 8 months			Positive **SVI**, Gross **ECE**		High-Teal / *Azure*
High		Any	PSA < 100; any PSADT			**N1**	BS (-)	Any
Royal								
		Any	>100	Any	Any			*Royal* = Any rising PSA with a low testosterone and / or any **mets** outside pelvic nodes
Low	Yes		<10			All scans clear		
Basic	Yes or No		<20			<6 **Mets**, 1 or more outside of pelvic nodes		
High			Any			>5 **Mets** with at least 1 outside pelvic nodes		

Appendix I.

Table of Five Stages of Blue

(opposite)

Rx. = Treatment; **MP-MRI** = Multiparametric MRI; **CDU** = Color Doppler Ultrasound; **CT** = CAT scan; ECE = Extracapsular Extension; **SVI** = Seminal Vesicle Invasion; **N1** = Pelvic Lymph Node Mets; "**Small**" = < 12 mm; **PSADT** = PSA Doubling Time; **PET** = C11 Axumin or PSMA; **XRT** = Radiation; **Testo** = Testosterone; **BS** = Bone Scan

Appendix II.

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 20 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 Tea*l, also known as *favorable Intermediate-Risk* prostate cancer is like *Low-Teal* except for having a higher number of biopsy cores with cancer, 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-Azur*e 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 8 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*. Appendix I 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.