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CASE MANAGEMENT

Treatment Options for Localized Prostate Cancer

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OBJECTIVES
After reading this article, the reader should be able to:

- Identify the major risk factors for prostate cancer.
- Discuss the controversy regarding the use of prostate-specific antigen levels to guide the initial treatment of prostate cancer.
- Summarize the long-term follow-up results of a major clinical trial assessing active monitoring, radical prostatectomy, and external beam radiotherapy plus concomitant androgen deprivation therapy for the management of prostate cancer.
- Delineate the goals of and appropriate patients for the focal treatment of prostate cancer.
- Compare and contrast cryotherapy and high-intensity focused ultrasound in the treatment of prostate cancer.

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A 72-year-old white male is referred to Indiana University Health after serum prostate-specific antigen (PSA) screening shows slightly elevated levels of 5.5 ng/mL. Multiparametric magnetic resonance imaging (mp-MRI) is performed *(Figure 1* *see page 2)* and used to direct a 12-sample transrectal ultrasound-guided prostate biopsy (TRUS-PB). Two samples taken from the right side of the gland demonstrate an intermediately aggressive prostate cancer (grade group 3, Gleason 7) *(Table 1* *see page 2)*. The patient is otherwise healthy; has no urinary issues; and experiences normal erections, using sildenafil to improve penile firmness. He and his physician discuss treatment options.

Overview of Prostate Cancer

Prostate cancer is the most common noncutaneous cancer among US males.[1] In 2016, nearly 181,000 new cases were diagnosed, and more than 26,000 men died from the disease. The strongest risk factors are age (rates increase until age 70 and decline thereafter), positive family history (having an affected first-degree relative elevates risk two-fold), and black race.[2] Black men not only have a higher incidence of prostate cancer, but they are more likely to be diagnosed at an advanced stage and die from the malignancy than are white men in every age group. An estimated one in five black males and one in six white males will be diagnosed with prostate cancer during their lifetimes, and in 2013 (the last year for which data are available), mortality rates were approximately 39 percent versus 20 percent, respectively.[3]

In the United States, 90 percent of prostate cancers are detected by PSA screening. Disease risk increases as the PSA level rises, from approximately eight percent for levels ≤1.0 ng/mL, to 25 percent for levels of 4.0 to 10 ng/mL, to more than 50 percent for levels >10 ng/mL.[4] Needle biopsy is used to establish the diagnosis, with TRUS-PB the procedure of choice for obtaining high-quality tissue cores for histopathologic assessment.[5] A 12-core extended technique is often preferred because of its ability to detect nearly one-third more cancers than the traditional 6-core (sextant) approach.[6]

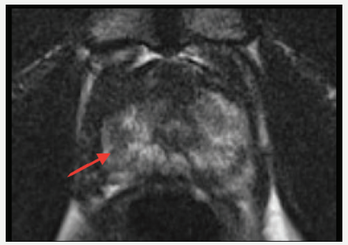

Figure 1. mp-MRI used to guide TRUS-PB

The arrow points to a small, right-sided prostate lesion.

TABLE 1. GRADE GROUP SCORING SYSTEM FOR PROSTATE CANCER[14]

Grade Group (Gleason Score)	Pattern Definition
1 (6: 3 + 3)	Individual, discrete, well-formed glands only
2 (7: 3 + 4)	Predominantly well-formed glands with a lesser component of poorly formed/fused/cribriform glands
3 (7: 4 + 3)	Predominantly poorly/formed/fused/cribriform glands with a lesser component of well-formed glands
4 (8: 4 + 4, 3 + 5, or 5 + 3)	Poorly formed/fused/cribriform glands only or • Predominantly well-formed glands with a lesser component lacking glands or • Predominantly lacking glands with a lesser component of well-formed glands
5 (9-10: 4 + 5, 5 + 4, or 5 + 5)	Lacks gland formation/necrosis with or without poorly formed/fused/cribriform glands

Management Options

The widespread use of PSA testing has resulted in a dramatic increase in the diagnosis and treatment of prostate cancer. Yet not every man receiving this diagnosis benefits from intervention, as the disease often progresses slowly and is not fatal. Autopsy series indicate that 30 percent of men older than 50 years of age and 70 percent older than 70 years have occult prostate cancer, with their deaths attributable to other causes.[7] Consequently, the optimal initial approach to early-stage prostate cancer detected on the basis of serum PSA levels remains unclear and controversial.

Active Monitoring and Standard Treatment

"Active monitoring, consisting of biannual PSA testing and mp-MRI together with periodic prostate biopsy, is an option for men with small, slow-growing tumors, indicated by a Gleason score of 6 or less," says Michael Koch, MD, professor and chairperson of the Department of Urology at Indiana University School of Medicine and urologist at Indiana University Health. "The risks associated with active monitoring may be somewhat mitigated by genetic testing to evaluate tumor aggressiveness."

Some form of treatment is generally recommended for reasonably healthy men with a life expectancy of at least 10 years who have higher Gleason scores or in whom genetic testing suggests that this score underestimates cancer risk. Standard interventions for clinically localized disease are radical prostatectomy; radiotherapy (external beam or brachytherapy); and androgen deprivation therapy (ADT), used alone or in combination with radiotherapy.

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Comparison of clinical outcomes. In the Prostate Testing for Cancer and Treatment (ProtecT) trial, funded by the National Institute for Health Research, 1643 men aged 50 to 69 years diagnosed with localized, low-risk prostate cancer were randomized to active monitoring, radical prostatectomy (primarily open retropubic procedures), or external beam radiotherapy (which included short-course neoadjuvant ADT).[8] At a median of 10 years, prostate cancer-specific mortality was low irrespective of the treatment assigned, with 17 deaths occurring overall and no significant differences among the groups. However, metastases developed more often in the active monitoring group (n=33), as compared with the surgery group (n=13) or radiotherapy group (n=16), and rates of disease progression were more than twice as high in the active monitoring group (n=112) versus the surgery or radiotherapy group (n=46 for each). Nonetheless, variation among the three groups did not result in significant differences in clinical outcomes, and even longer follow-up is needed to reach definitive conclusions.

Patient-reported outcomes. A comparison of patient-reported outcomes over six years for the ProtecT study participants found that prostatectomy had the greatest negative effect on urinary continence and sexual function, particularly erectile function, although some recovery occurred over time.[9] Radiotherapy had little impact on urinary continence, and its negative effect on urinary voiding, nocturia, and sexual function was greatest six months after treatment, then mostly (urinary issues) or somewhat (sexual function) resolved by 12 months. Urinary and sexual function declined gradually in the active monitoring group. Bowel function was worse in the radiotherapy group at six months but improved thereafter and was unchanged in the other groups.

Focal Therapy

"The location of the prostate—between the bladder and penis, immediately anterior to the rectum, and surrounding the urethra—translates to a high risk for injury when surgery or radiotherapy is performed to remove or ablate the entire gland," Dr. Koch explains. "Focal therapy is an emerging treatment option for prostate cancer. Its goal is to combine tumor control with minimal damage to surrounding structures, in particular the external urinary sphincter, bladder neck, neurovascular bundles, and rectum, thereby reducing side effects and preserving a patient's quality of life."

Although focal therapy can be used to treat the entire prostate, Dr. Koch says it is best-suited for the ablation of small, unilateral lesions, estimated to account for 20 to 40 percent of all prostate cancers.[10] Aside from focal interstitial radiotherapy (brachytherapy), the two most frequently used focal techniques for prostate cancer are cryotherapy and high-intensity focused ultrasound (HIFU).[11] Other strategies (not described) include laser

ablation, photodynamic therapy, irreversible electroporation, and radiofrequency ablation.

Cryotherapy. Cryotherapy, performed under general or spinal anesthesia, uses TRUS to place ultrathin cryoprobes within the prostate via the perineum. Argon gas rapidly creates an "ice ball" that disrupts cell membranes in the targeted area, resulting in cell death. Temperatures as low as -40° C may be necessary to ensure complete freezing of the intracellular compartment. A warming catheter is used to prevent urethral freezing, and probes placed in and around the prostate monitor rectal wall and urinary sphincter temperatures to minimize side effects (e.g., incontinence, rectal fistula). Two freezing cycles are usually performed, with the prostate allowed to thaw passively or actively (using helium gas) in between cycles. After the final thaw, a urinary catheter is inserted and left in position for a few days. Patients typically recover within one week.

A meta-analysis and systematic review found that cryotherapy is a relatively effective method for clinically localized prostate cancer, can be repeated if necessary, and has survival rates comparable to radical prostatectomy and radiotherapy.[12] However, because of the difficulty conforming the cryoprobes to the shape of the prostate—especially to lesions located in the posterior portion of the gland—the sexual, urinary, and bowel complications associated with standard treatment may also occur with cryotherapy.

HIFU. HIFU is a noninvasive treatment that causes cell death through two physiologic mechanisms.[11] First, the energy of the ultrasonic waves is absorbed by the target tissue and converted to heat, resulting in coagulative necrosis. Second, inertial cavitation is caused by alternating cycles of compression and rarefaction.

HIFU is administered through a transrectal ultrasound probe *(Figure 2)* that raises

Figure 2. HIFU targeted prostate ablation device

A. *The HIFU probe is immobilized by a device attached to the surgical table.*

B. *The concave transducer alternates between imaging the prostate and delivering high-energy ultrasound to destroy tissue. The transducer moves side-to-side, proximally, and distally to treat the targeted areas.*

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"The US Food and Drug Administration (FDA) has approved two HIFU devices for ablation of prostate tissue but did not specifically approve it for the treatment of prostate cancer."

tissue temperature at the focal point to almost 90° C (195° F). The device fuses mp-MRI data to real-time ultrasound images, thereby allowing precise tissue targeting that avoids damage to adjacent normal tissue.[13] Although such restricted ablation increases the risk for recurrence, Dr. Koch says that HIFU can be used to retreat an area as well as for *de novo* ablation in another segment of the prostate.

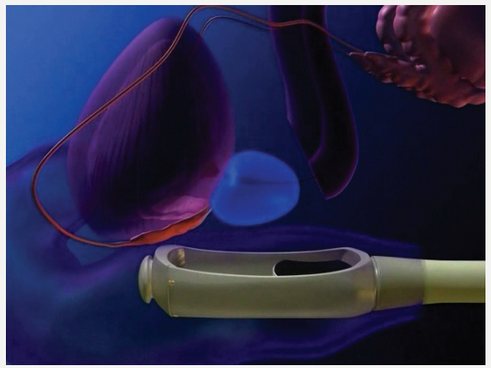
One limitation to HIFU is that the tool can only penetrate four centimeters into the rectum, precluding its use for deep-seated lesions in large prostates. However, the major drawback to this form of focal therapy at the present time is that its cost is not covered by insurance, including Medicare, and patients must pay for the procedure out-of-pocket.

"The US Food and Drug Administration (FDA) has approved two HIFU devices for ablation of prostate tissue but did not specifically approve it for the treatment of prostate cancer," reports Dr. Koch. "This situation mirrors that of cryotherapy and lithotripsy several years ago, where insurance coverage was denied until both procedures achieved wide acceptance. Urologists are hopeful that in the near future, as the use of HIFU for the treatment of prostate cancer becomes more mainstream, the FDA will expand its approval."

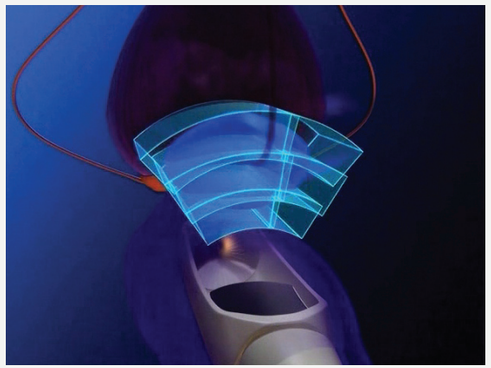
The patient is not comfortable with active monitoring and is concerned that standard therapy will impair his remaining sexual functioning and cause incontinence. He elects to undergo HIFU with the understanding that it may not be as effective as total prostate removal or ablation. The two-hour outpatient procedure is performed under general anesthesia *(Figure 3* *see page 6**)*. At its completion, a urinary catheter is placed, and following a brief stay in recovery, the patient is discharged to a local hotel (he lives in another state). Over the next two days, he keeps in regular email contact with Dr. Koch and reports no pain or other problems. The catheter is removed 48-hours post-procedure, and the patient returns home the following day. One week after treatment, he emails that he is playing golf and engaging in sexual activity.

At six-month-follow-up, the patient describes minor spotting and decreased urinary flow that persisted for a few weeks after HIFU and has totally resolved. Serum PSA testing shows his level has declined to 2.4 ng/mL, and mp-MRI demonstrates the treated area has involuted. Biopsy results are normal except for a tiny focus of non-aggressive cancer on the left (opposite) side that will be closely monitored. Another PSA and mp-MRI are scheduled 12 months after treatment and will be repeated again 18 months post-procedure, at which time another biopsy will also be done.

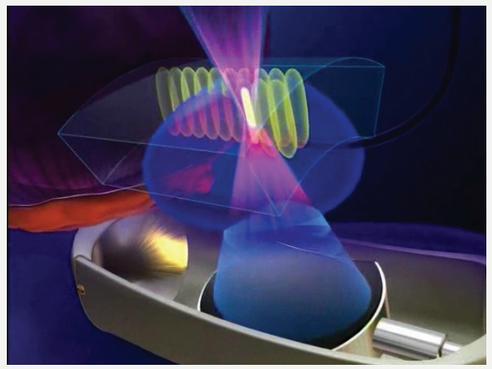
Figure 3. HIFU procedure

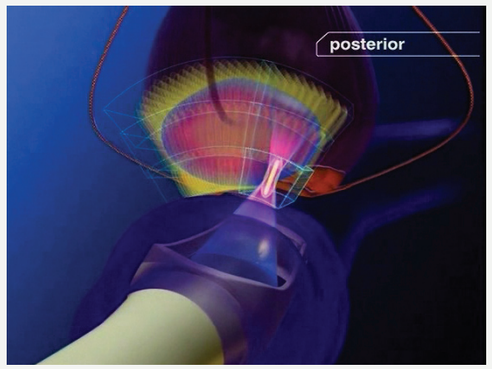


Image—*Transducer in the probe aquires images of the prostate.*



Plan—*Physician plans, or maps out, what tissue to target.*





Treat—*Small lesions are created in the prostate at the focal point. This is repeated until all targeted tissue is destroyed.*

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"Focal therapy with HIFU is associated with improved preservation of erectile function and urinary continence compared with standard therapy," concludes Dr. Koch. "Nonetheless, additional data from large trials are required before its ultimate role in the management of prostate cancer can be determined."

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Dr. Koch received his medical degree from Dartmouth Medical School in Hanover, NH, did his residency training in general surgery at the Dartmouth-Hitchcock Medical Center and in urology at the Vanderbilt University Medical Center in Nashville, TN, and completed a surgical research fellowship at Dartmouth Medical School. His clinical interests are focused on urologic cancer and complex reconstruction of the urinary tract.

Dr. Koch has served as professor and chairperson of the Department of Urology at IU School of Medicine since 1998. He is past-president of the Urology Chairpersons Group and the Society of Academic Urology, past-president and trustee of the American Board of Urology (ABU), past-chair of the ABU residency review committee for urology, and past-chair of the joint examination committee of the ABU and the American Urological Association. He is currently the urology representative to the American Joint Committee on Cancer.

The author of more than 250 peer-reviewed publications, including a report on the first clinical trial of HIFU, Dr. Koch is recognized internationally as an expert in the treatment of bladder and prostate cancers. He has extensive experience with robotic surgery for prostate cancer, performing more than 180 robotic prostatectomies each year. He also serves as the principal investigator for several ongoing urologic cancer clinical trials.

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