

HIFU as a Logical Middle Ground

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As far back and ancient times, great philosophers recognized balance as a rational means to a good life. They called it by different names—The Golden Mean, The Doctrine of the Mean or The Middle Way—but the principle is the same. If there were a clinically and economically balanced approach to detecting and treating prostate cancer, what would it look like? While global experts seek the answer to this riddle, the lack of professional consensus on when or what treatment is needed can be very perplexing for patients. The four topics up to this point reveal areas that are approaching balance in prostate cancer screening, diagnosis and treatment. The pendulum is still swinging—but seems to be narrowing in toward the center.

The first article looked at the broad sweep from a time during which prostate cancer often went undiagnosed and became life threatening, to the PSA era in which demographics have swung toward diagnosis in younger men. During the same period, the predominant treatments of radical surgery and radiation have improved, but still carry risks of urinary and sexual aftereffects that make decision-making tough for many men.

The second article on technology showed how advances in diagnosis and treatment have resulted in more accurate disease identification at earlier stages, and a parallel development in less invasive, image-guided treatments with reduced risk of side effects.

The third article discussed clinical breakthroughs suggesting that not all prostate cancer is clinically significant (requiring immediate treatment). This calls into question whether radical (whole gland) treatments are necessary in every case. Precise tissue-sparing treatments for qualified patients appear to be safe, effective, and able to preserve urinary and sexual function. Improved imaging can be used to monitor for disease recurrence, giving ample warning if a suspicious site is revealed.

The fourth article examined policy and clinical challenges in the effort to reduce the economic costs of screening and overtreatment, while not putting patients at risk of undetected disease growing in their bodies.

Identifying a logical middle ground

Taken together, these articles suggest some criteria to illuminate a logical middle-ground approach to diagnosing and treating prostate cancer.

1. *Less invasive, early, accurate diagnosis.* As improved biomarker tests are becoming available, they provide a better way to evaluate if further testing is truly indicated, thus avoiding a rush to biopsy (overdetection). If so, imaging by expert readers, especially 3T MRI or color Doppler ultrasound, offers a way to determine if a patient should be biopsied. In most cases, a biopsy can potentially be targeted

into a suspicious area revealed by imaging. **Advantages include:** a) fewer patients sent for biopsies due to ambiguous PSA readings; b) reduced number of biopsy needles with less risk of infection and side effects; c) needle samples taken from a central location most likely to harbor aggressive disease, giving a more accurate diagnosis; d) earlier diagnosis of localized disease, allowing the widest array of treatment choices and time to decide; e) may be a more efficient use of medical dollars by eliminating random overtesting, and matching treatment with disease to avoid overtreatment.

2. *Availability of minimally invasive ablation treatments.* Ablation, or destruction of tumors within the body, is the nonsurgical equivalent of removing diseased tissue. It is accomplished by delivering a lethal amount of thermal energy (heat or cold) to destroy cancerous tumors plus a margin of safety. Methods of prostate cancer ablation currently in use and/or in clinical trial include High Intensity Focused Ultrasound (HIFU), cryoablation (cryotherapy or freezing), laser ablation, photodynamic ablation, irreversible electroporation (IRE), and radiofrequency (RF) ablation. **Advantages include:** a) outpatient procedure with minimal time under general anesthesia; b) real time image guidance assures precision and immediate verification of the zone of destruction; c) safety mechanisms built into the equipment and software protect adjacent structures from overtreatment; d) reduced risk of side effects due to healthy tissue preservation.
3. *At least five years of published data showing balance between effectiveness and quality of life.* Of the ablation methods listed above, only two (cryoablation and HIFU) meet this standard. Both have demonstrated comparable cancer control rates with radical prostatectomy, especially as technologies have improved, and favorable side effect profiles. For example:

	RP	Cryoablation	HIFU
Biochemical disease-free survival at 5 yrs	68-98% ^{1, 2}	50-92% 87-98% negative biopsy ³⁻⁴	55-95% 55-98% negative biopsy ⁵⁻¹³
Incontinence	9-20% ¹⁴	3-10% ¹⁵	0-10% ⁵⁻⁷
Erectile Dysfunction	4-85% ^{8,9}	40-100% ¹⁵	8-50% ^{8,9}

Advantages include: a) increased confidence in the clinical track record; b) greater number of experienced physicians who offer the treatment.

4. *Can be done as a focal treatment for qualified patients.* Some patients who are candidates for Active Surveillance because of a low disease risk level may not be comfortable living with a small focus of disease that may become more active in the future. Focal ablation, or targeted treatment, offers a rational. **Advantages include:** a) rational middle ground between radical treatment vs. no treatment; b) individualized to patient's medical and psychological needs; c) repeatable if

¹ Mullins JK, Feng Z, Trock BJ, et al. The impact of anatomical radical retropubic prostatectomy on cancer control: the 30-year anniversary. *J Urol* 2012;188:2219-24.

² Loeb S, Zhu X, et al. Long-term radical prostatectomy outcomes among participants from the European Randomized Study of Screening for Prostate Cancer (ERSPC) Rotterdam. *BJU international* 2012.

³ Cheetham P, Trussdale M, Chaudhury S, Wenske S, Hruby GW, Katz A. Long-term cancer-specific and overall survival for men followed more than 10 years after primary and salvage cryoablation of the prostate. *J Endourol* 2010;24:1123-9.

⁴ Jones JS, Rewcastle JC, Donnelly BJ, Lugnani FM, Pisters LL, Katz AE. Whole gland primary prostate cryoablation: initial results from the cryo on-line data registry. *U Urol* 2008;180:554-8.

⁵ Uchida T, Ohkusa H, Nagata Y, Hyodo T, Satoh T, Irie A. Treatment of localized prostate cancer using high-intensity focused ultrasound. *BJU international* 2006;97:56-61.

⁶ Uchida T, Ohkusa H, Yamashita H, et al. Five years experience of transrectal high-intensity focused ultrasound using the Sonablate device in the treatment of localized prostate cancer. *Int J Urol/Japanese Urological Association* 2006;13:228-33.

⁷ Muto S, Yoshii T, Saito K, Kamiyama Y, Ide H, Hori S. Focal therapy with high-intensity-focused ultrasound in the treatment of localized prostate cancer. *Japanese J Clin Oncol* 2008;38:192-9.

⁸ Ahmed HU, Zacharakis E, Dudderidge T, et al. High-intensity-focused ultrasound in the treatment of primary prostate cancer: the first UK series. *Br J Cancer* 2009;101:19-26.

⁹ Inoue Y, Goto K, Hayashi T, Hayashi M. Transrectal high-intensity focused ultrasound for treatment of localized prostate cancer. *Int J Urol/Japanese Urological Association* 2011;18:358-62.

¹⁰ Uchida T, Shoji S, Nakano M, et al. Transrectal high-intensity focused ultrasound for the treatment of localized prostate cancer: eight-year experience. *Int J Urol/Japanese Urological Association* 2009;16:881-6.

¹¹ Sumitomo M, Hayashi M, Watanabe T, et al. Efficacy of short-term androgen deprivation with high-intensity focused ultrasound in the treatment of prostate cancer in Japan. *Urology* 2008;72:1335-40.

¹² Sumitomo M, Asakuma J, Yoshii H, et al. Anterior perirectal fat tissue thickness is a strong predictor of recurrence after high-intensity focused ultrasound for prostate cancer. *Int J Urol/Japanese Urological Association* 2010;17:776-82.

¹³ Dudderidge T, Ahmed H, Emberton M. High-intensity focused ultrasound for localized prostate cancer: initial experience with a 2-year follow-up. *BJU international* 2009;104:1170-1; author reply 1.

¹⁴ Hu JC, Gu X, Lipsitz SR, et al. Comparative effectiveness of minimally invasive vs open radical prostatectomy. *JAMA* 2009;302:1557-64.

¹⁵ Shelley M, Wilt TJ, Coles B, Mason MD. Cryotherapy for localised prostate cancer. *Cochrane Database Syst Rev* 2007;CD005010.

- necessary; d) keeps other future treatment options open if necessary.
5. *Salvage treatment is an option for patients with radiation-recurrent prostate cancer.* Despite refinements in radical prostatectomy, including less invasive robotic-assisted surgery, most urologists agree that salvage prostatectomy is a difficult procedure. However, if the recurrent disease is still localized, i.e. has not escaped the prostate capsule, ablation may be a potentially curative alternative to going on hormone therapy.

HIFU as a Golden Mean

HIFU stands up well as a logical and balanced response to the needs of today's patients.

- A. In the changing prostate cancer landscape where younger men are diagnosed with localized prostate, their needs and desires include minimal time off of work, quick return to normal activity, and good cancer control with minimal risk of urinary and sexual side effects. HIFU, with 15 years of supportive published data, is gaining consideration from patients who are concerned about the aftereffects of surgery or radiation. For older patients who may not be candidates for surgery, the minimalist outpatient treatment with less impact on genitourinary function may be a good alternative to weeks of daily radiation treatments.
- B. HIFU is safe, effective and available. The lethal heat generated by the precisely targeted and shaped sonic energy is immediately destructive of tumor tissue. The ability to monitor temperatures and changes in tissue, in real time, gives confidence that the zone of destruction, whether whole-gland or focal treatment, is exactly what is intended. HIFU is finally FDA-approved for prostate ablation within the U.S.
- C. HIFU now has at least 15 years of published data in international journals. As the technology has evolved, statistics reflect improved cancer control as well as reduced incidence of short-term side effects. Refer to the brief table in Number 3 above for sample statistics.
- D. HIFU can be performed as a focal treatment for qualified patients. Dr. Stephen Scionti has been one of the leading pioneers in the field of Focal MRI Fusion Guided HIFU treatment and has the largest experience with this technique in the United States.

Conclusion

HIFU is a logical treatment consideration for the following types of patients. Those who are diagnosed with low-to-moderate risk localized prostate cancer may seek a "Middle Way" or "Golden Mean" between radical whole-gland treatments and observation as a way to buy time before treatment. Those who are drawn to Active Surveillance, including lifestyle changes in diet, exercise, etc. may discuss with their doctors the merits of a focal HIFU treatment as a way to destroy the tumor while preserving their healthy prostate tissue, urinary and sexual function. Those whose cancer has come back after radiotherapy (external beam or seed implants) may logically consider a HIFU ablation as a potentially curative alternative to hormone therapy.

If Socrates, Plato, Aristotle or Confucious were alive today, perhaps they would agree that HIFU meets their tests for a balanced Middle Way.