Clinical Breakthroughs: HIFU

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Winston Churchill once remarked, "To improve is to change; to be perfect is to change often." Medical science regarding prostate cancer is not yet perfect, but it is certainly changing continually.

Let's look at recent improvements in clinical knowledge. The most pertinent advances are: a) earlier diagnosis, b) definition of clinically significant vs. insignificant tumors, and c) precise identification of small, confined masses through imaging. Each of them is influencing the new worldview of personalized cancer care in important ways.

Earlier diagnosis: beyond PSA

Generally, early diagnosis results in improved chances of complete cure. Cancer patients who had successful treatment never wish their cancer had been found later. Even if the treatment has lingering side effects, as long as it was effective, patients come to terms with the situation. Treatment trade-offs may be a fact of life until the day comes when cancer is preventable. But there's good news: thanks to finding prostate cancer when it's still early and localized, ablation technologies like HIFU can preserve as much healthy tissue as possible, offering tumor destruction with minimal-to-no side effects.

Today's imaging can show the size, shape and location of prostate tumors. Unlike the ultrasound used by urologists in their office, magnetic resonance imaging (MRI) shows good contrast of normal and abnormal tissue within the prostate. Patients with an elevated PSA and/or abnormal DRE may want to go for MRI imaging to determine if a biopsy is needed. While some urologists may resist the request for a referral to an imaging center, most now support the idea of acquiring more specific information before scheduling a biopsy. In a sense, pre-biopsy images are like the NORAD (North American Aerospace Defense Command) early warning system. Detecting an enemy's approach (suspicious mass) buys time to gain correct information (biopsy), strategize a plan if it's truly an attack (explore treatment options), and implement it if needed (get treated). In the case of prostate MRI that shows a possible malignancy, most urologists do prefer to do their own biopsies, but some may agree to the radiologist doing a targeted biopsy under the MRI. The earlier acquired scan, coupled with real-time MRI, guides selective placement of a few needles into the tumor's core. Together with MRI imaging, the laboratory analysis (pathology) of the tissue samples offers a comprehensive diagnosis of the size, shape, location and aggressiveness of any cancer found. Thus, early stage cancer can be efficiently detected, depicted and diagnosed.

Since prostate cancer falls under the medical specialty of urology, most patients prefer to work with their own urologist for the biopsy. An innovation called Image Registration (Fusion or co-registration) keeps prostate biopsy in the realm of urology but has the same precision as an MRI-guided biopsy. As described in the previous article on technology,

fusion blends the MRI and ultrasound prostate images to create a virtual 3D image of the gland's exact size and shape that also shows the suspicious area. It's similar to some of the special effects that amaze movie audiences, only applied to medicine. Urologists equipped with this software can now do the same targeted biopsy as a radiologist, and send the tissue samples for the same accuracy of diagnosis at a cellular level.

Thus, prostate cancer is being diagnosed early, with less biopsy discomfort, almost no room for error, and therefore fewer repeat biopsies. Cancer that is found when it is small and milder than it may eventually become is permits a wide range of choices including minimally invasive ablation with fewer side effects, or Active Surveillance.

Clinically insignificant vs. significant disease

Another forward-looking development is the evidence that not all tumors are equally dangerous. Prostate cancer was traditionally believed to be multi-focal (many locations of cancer throughout the gland). It now appears, however, that very small clusters of cancer cells may remain dormant, perhaps indefinitely. If they never grow and spread, they are *clinically insignificant* and can be monitored over time. But what if there are malignant cells that are mutating (changing) in an aggressive direction? The theory is that the tumor with the largest volume is primary and usually determines the biology of the disease. It is called the *index lesion* and is considered more worrisome because it may contain *clinically significant* prostate cancer. What does that mean?

According to *Molecular Biology of the Cell,* "Even when a cancer has metastasized, its origins can usually be traced to a single primary tumor, arising in an identified organ and presumed to be derived by cell division from a single cell that has undergone some heritable change that enables it to outgrow its neighbors."[i] In other words, it's a tumor that likely contains a mutated aggressive cell that can clone itself and spread. While there is not yet universal agreement on the criteria that determine "significance," Gleason 3+4 or greater is generally considered clinically significant, and the Gleason score often correlates with the size of the tumor, length of the positive biopsy core, PSA, tumor stage, or other factors to further validate the assessment. Genomic testing of cancer cells also can help to identify cancers with aggressive behavior that are "clinically significant."

Thus, *clinically significant* suggests a need for treatment as a "pre-emptive strike" against a potentially dangerous cell line. (Note: while the index lesion is the most likely origin of rogue cells, there are reported cases in which miniscule, presumably insignificant tumors have spawned aggressive disease, further underscoring the need for routine monitoring.) The development of clinically significant cancer is also another reason to diagnose cancer early, before it has progressed to a higher threat level.

Must patients with clinically significant and/or multifocal disease necessarily have a whole-gland treatment? A 2012 study pursued the issue as to whether only unifocal (single tumor) disease qualified for a focal (targeted) treatment, or could those with an index lesion accompanied by other very small "nonindex elements" also have a focal treatment of the index lesion leaving nonindex sites untreated. The authors concluded that

under certain careful conditions having to do with clinical significance, some multifocal patients were possible candidates for focal treatment, similar to unifocal patients. [ii]

The concept of clinical significance/insignificance lays the logical groundwork for a cancer management strategy that involves a minimally invasive ablative focal treatment such as HIFU, followed by an Active Surveillance approach of manage-and-monitor. Patients must have as much accurate information and frank discussion with their physician as possible to determine the nature and extent of their disease. For those who qualify clinically (and psychologically, as not everyone is comfortable with the idea of less than radical treatment), such a strategy destroys the primary tumor while leaving future treatment options open; at the same time lifestyle changes after treatment can minimize the odds of the cancer coming back—with imaging as a safety net to identify any new activity of small, early lesions.

Specialized imaging detects and tracks small, early masses

Finding and observing tiny lesions is like espionage. You want highly trained agents with top devices. The clearest MRI images come from the most powerful magnets. MRI field strength is measured in units of Tesla, or T, and the higher the number, the greater the T. Until recently, most MRI machines were 1.5T, but the latest technology now becoming more widely available is 3T MRI. Increased power also reduces scanning time, which helps keep patients more comfortable during the process.

Just like agents use highly sensitive microphones, powerful lenses, night vision goggles etc., to observe their target, scans done by these powerful magnets can be further enhanced by multiparametric ("many parameters") techniques such as Diffusion-Weighted Imaging (DWI), T2-weighted imaging, spectroscopy and dynamic contrast sequences. While it is beyond the scope of this article to describe each one, the important point is that singly or in combination they are like highly trained spies detecting telltale signs of activity. Research comparing MRI images done before prostatectomy with the actual removed glands has demonstrated a high rate of matching locations, even with small tumors,[iii] increasing confidence in the detection accuracy of prostate imaging especially when interpreted by an experienced reader.

Can imaging alone diagnose prostate cancer? Experts agree that we're not quite there. While a method like DWI can produce images that correlate with aggression levels proven by biopsy, urologic standards of care do not support proceeding with treatment unless cancer is diagnosed by tissue examination in the lab.

In any event, early detection and diagnosis through imaging—and the understanding of clinical significance—gives more knowledge of an individual's cancer than ever before in history. This is true in many other cancers besides prostate cancer. As patients continue to seek out the least invasive treatment that will destroy their cancer without destroying their lifestyles, the clinical community is meeting them more than halfway with image-based target-and-manage treatment plans based on early detection and accurate clinical information.

The earliest comprehensive knowledge a patient can gain about his prostate cancer frees him from irrational fears, and assists him in making reasoned choices about which path is right for him: a conventional whole-gland treatment, a minimally invasive whole-gland ablation such as HIFU, a targeted or focal ablation, or holding off on treatment in favor of Active Surveillance. Early detection, clinical significance, and image monitoring are key factors in a logical decision.

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[i] Alberts B, Johnson A et al. Molecular Biology of the Cell. 4th edition. New York: Garland Science; 2002. Cancer as a Microevolutionary Process. Available from: http://www.ncbi.nlm.nih.gov/books/NBK26891/

[ii] Karavitakis M, Ahmed HU et al. Anatomically versus biologically unifocal prostate cancer: a pathological evaluation in the context of focal therapy. Ther Adv Urol. 2012 Aug;4(4):155-60.

[iii] Rosencrantz AB, Deng FM et al. Prostate cancer: multiparametric MRI for index lesion localization--a multiple-reader study. AJR Am J Roentgenol. 2012 Oct;199(4):830-7.