Biopsy Procedures are on the Rise

RECENT DATA FROM Bostwick Laboratories indicates a growing trend in the number of cores taken during a biopsy session has increased from an average of 8 to18 over the past 12-18 months. The most troubling part of a biopsy procedure is that it is a blind procedure, whereby; there are no specific targets to hit. Equally troubling is that biopsies performed in this manner are rife with failure secondary to sampling bias resulting in false negatives. Even more alarming is the fact that saturation biopsies (upwards of 90 biopsies in a single biopsy session) are recommended to determine cancer sites for focal therapy. Saturation biopsy or prostate mapping is a process whereby tissue samples are taken at 0.5 cm intervals throughout the prostate. Given what has been discussed, the rhetorical question needs to be asked, **"Is is possible to cure a patient with focal therapy once saturation biopsies have been performed?"** To Cryosurgeons across the country and around the world, the consensus opinion is astonishingly . . . yes. How can it be that Cryosurgical Physicians around the country preferentially suggest Cryosurgery, a treatment that freezes the prostate with Argon gas, as an acceptable means to ablate prostate cancer cells locally despite the fact that countless cells have escaped the capsule? The unwitting public needs to understand the facts before they will be adequately

prepared to accept the consequences inherent in this diagnostic exercise. While only time will tell how well individuals will perform from the implementation of this form of therapy; adding saturation biopsy to the equation adds an additional unacceptable risk of 'needle tracking', likely contradicting the concept for cancer cure.

A far better and therefore more patient friendly approach to the biopsy conundrum would be to allow a 3.0 Tesla MRI scan with its various sequences to evaluate patients preferentially prior to a targeted biopsy. The advantages are many including the ability for up to 70-80% of patients to avoid a biopsy altogether when no suspicion of cancer is identified. These individuals can be treated for prostatitis with the expectation that their PSA levels will remain low and non-progressing. In those individuals where a lesion is found, targeted biopsies can be administered to a specific localized region of interest (ROI) resulting in fewer needle punctures. In my practice, in an effort to decrease, if not eliminate 'needle tracking', I recommend a protocol that utilizes an anti-androgen such as Casodex® (Bicalutamide) at 150 mg per day for a specific time frame. Casodex® blocks a receptor on the nucleus of the prostate cell, preventing Testosterone and Dihydrotestosterone from attaching, thereby, promoting cell death. While further studies are encouraged, this is a good start to an otherwise enigmatic clinical scenario that begins to unravel for the patient biopsied, at the point of needle contact. **Given the fact that High Intensity Focused Ultrasound (HIFU) is approved in the USA for uterine fibroids (a benign condition in women) and ostensibly very safe in the hands of the most skilled, albeit few, Urologists, the HIFU technology should be suitable for biopsy negative patients with a rising PSA (a most common scenario), MRI validated disease (cancer) in patients with a rising PSA or men with intractable prostatitis referencing that Arnon Krongrad is performing**

radical prostatectomy in Miami on men without evidence of cancer but rather longstanding prostatitis only.

Significant Biopsy Related Studies

Given the significant risks of a biopsy procedure to the patient, attention should be placed on doing fewer biopsies while saturation biopsies should rarely if ever be utilized. In a retrospective study, Grosslaus and colleagues evaluated the difference between a sextant biopsy (6 cores) and a greater number of biopsies relevant to the final pathology at surgical intervention. Specifically, 135 consecutive patients who underwent a radical retropubic prostatectomy were studied regarding number of cores, percentage of positive cores, laterality of positive cores and Gleason score. Their findings noted **no significant relationship between the number of cores obtained and the predicted pathology of the radical prostate specimen.** Furthermore, there was no difference in the number of positive cores, bilateral positive cores or the percentage of tumor in the cores when more than 6 cores were taken. While it was noted that the percentage of positive cores may be the best predictor of pathological stage and tumor volume, **there appeared to be no improvement in prognostic information when more than 6 cores were taken.**

Sur and colleagues conducted a prospective study comparing minimal biopsies to a 24 core biopsy. While there was a suggestion that a 6 core biopsy may not be enough in certain cases, **the 24 core biopsy did not improve cancer detection rates.** There conclusion was that saturation biopsies should not be routinely performed preferentially when prostate cancer is suspected and that **24 biopsies did not outperform a 10 biopsy protocol. Fleshner and Klotz echoed the sentiments that saturation biopsy rarely if ever improved the cancer yield**

when they utilized their standard biopsy technique. Using MRI-Spectroscopy to guide where the needles are strategically placed, as few as 1 or 2 biopsies can isolate a cancer, minimizing cost, trauma and risk potential.

Meng and associates have noted that while increasing the number of cores taken at the time of biopsy may increase the number of cancers identified, **there is increasing recognition that many men with prostate cancer may not benefit from early aggressive intervention and that over-detection of prostate cancer has resulted in over-treatment.** Utilizing the Cancer of the Prostate Strategic Urologic Research Endeavor database, 4072 men with 6 or more biopsies were compared. 30% of the men had 6 biopsies, 47% of men had 7-11 biopsies, while 24% of men had more than 12 biopsies. Interestingly, there was a significant correlation noted between the number of biopsies performed and numerous sociodemographic and clinical variables including PSA, comorbidities and income. When this data was assessed by Kattan and Caner for prostate risk assessment scores, **there appeared to be no difference among men with a biopsy number between 6 and 17.** In a subset of men who underwent radical prostatectomy, there was no difference in the biochemical-free survival at greater than 2 years.

An article found on the American Cancer Society's website and published in the Journal of Urology, presents a point-counterpoint debate regarding saturation biopsy. According to Dr. Michael Lieber lead author from the Mayo Clinic study, 224 men who were previously biopsied as negative or with a precursor lesion like high grade prostatic intraepithelial neoplasia (HGPIN) and/or a change in digital findings underwent a saturation biopsy with upwards of 45 needle cores. The results of this biopsy technique

resulted in finding 34% patients (N=77) with prostate cancer. Dr. Lieber, speaking for the Mayo Clinic Urologists, states, "our perspective is, if you're going to biopsy them again (referring to the patients in question), why not use a better (more aggressive) technique initially?" Perhaps, neither Dr. Lieber nor his team of physicians recognizes the grave dangers associated with the biopsy technique. Fray Marshall, M.D., Professor and Chairman of the Department of Urology at Emory University School of Medicine had a little different take on the process. **"After a while, it's overkill.** If you have to biopsy every few millimeters of the gland, it seems like **it would be a bit excessive.**" Dr. Marshall does not agree with a blanket application of saturation biopsies. Despite the fact that Mayo Clinic's position is that 87% of cancers found were significant, this opens a debate on what constitutes significant? **Certainly, if you can qualify a patient for a radical procedure, it is easier to define the cancer as significant.** Dr. Marshall questions the significance of a cancer that requires 40 plus biopsies to find. **"Because prostate cancer is slow growing, older men with such small cancers could be harmed more than helped by treatment, leading some to choose a "watch and wait" approach."** Similarly, a chronic disease management (**CDM**) approach makes sense as it represents an academic strategy against prostate cancer. Dr. Lieber admits that some small cancers will be found (with saturation biopsies) but believes small cancers may be significant. He admits that saturation biopsies are bound to be more expensive, but he has **"no trouble with insurance (company) reimbursement". Hmmmm!**

The following patient case presentation speaks to the various clinical modalities utilized at our Center relevant to the diagnosis of prostate cancer including how we apply the biopsy procedure. This presentation also introduces 3.0 Tesla

MRI-Spectroscopy as the art form to take the guess work out of the biopsy procedure. In effect, an MRI-Spectroscopy scan will establish an all important roadmap for where disease lies.

Merlyn Freeman is a 51 year male from Canada with a PSA of 2.1 ng/ml. On digital rectal exam (DRE), his physician felt something on his prostate. Concerned, the patient saw his local Urologist who recommended a biopsy. Needing time to research this topic, Merlyn postponed the biopsy procedure, needing verification that a biopsy procedure was absolutely necessary. In need of a second opinion, Merlyn scheduled an appointment at the Scottsdale, Arizona—Mayo Clinic. The Urologist at the Mayo Clinic examined Merlyn's prostate and suggested that there was a 50% chance a biopsy would yield a cancer. As Merlyn's research continued, he utilized the Internet evaluating every aspect of the biopsy procedure. His concern that a biopsy would allow cells to escape the prostate was particularly unsettling to him. **When he spoke with his Physician Consultants, they denied any association of biopsy with the spread of cancer cells, despite a reference to an article in the Urologist's most prestigious journal.** Intuitively, the inability to spread cancer cells (if encountered), made no sense to Merlyn. As his Internet research continued, he ran across an article that identified the Diagnostic Center for Disease™ which believed as he that needle tracking takes place with virtually every biopsy. Following a free 30 minute conference call with the Medical Director, Merlyn scheduled a formal visit to the Center.

Merlyn scheduled a comprehensive visit at the center to review all aspects of his genitourinary system. Due to my keen interest and expertise in prostate disease, I welcomed the opportunity to offer a third opinion. While examples of a comprehensive visit at our Center are available throughout this book, I will elaborate

on Merlyn's clinical markers herein. Merlyn's PSA test result was noted at 2.1 ng/ml in March 2007. Historically, his PSA had been recorded at 1.73 ng/ml in June of 2005, followed by a PSA of 1.95 ng/ml in December 2006. A progressive rise in PSA, regardless of how small, is never a good sign and minimally imparts a 20-30% risk for prostate cancer. A family history of prostate cancer in his Father and brother supported a strong genetic link. A Uroflow test noted an adequate, if not normal, voiding trial while emptying 238 milliliters (1cc = 1ml) with a 10 cc per second average flow and a 21 cc per second peak flow rate. The post void residual was 37.4 ccs consistent with normalcy. The prostate exam noted a relatively small prostate with a defined area of interest on the left side. Based on my 20 plus years as a Urologist, it was my expressed opinion the patient had a 95% chance that prostate cancer was present. An expressed prostatic secretion (EPS), produced during the prostate exam, noted white blood cells throughout the specimen ranging from 10 to 160 per high powered field (400X—microscopically), consistent with non-bacterial prostatitis. Fewer than 10 white blood cells per high powered field would be consistent with normalcy. Prostatitis has been demonstrated to lead to the evolution of prostate cancer as noted by the American Association of Cancer Research (AACR), David Bostwick and others.

Next, an ultrasound was performed. Gray scale ultrasound identified a 24 cc prostate with an area of hypoechogenicity laterally in the left hemi-prostate. Areas of hypoechogenicity are areas that are less echogenic or darker. A visual for hypoechogenicity is to shine a flashlight at a tree during the nighttime hours. The beam will transmit well at the tree and on either side of the tree while remaining dark behind the tree. The area of darkness is analogous to a hypoechogenic or hypoechoic area seen in the prostate. In the prostate, areas that are

hypoechogenic may be cancerous approximately 20% of the time according to research data from UCSF and others. The remainder of the prostate noted scattered punctate (tiny) calcification throughout as a visual reminder of the inflammation present. Color Flow Power Doppler was then applied to the prostate. Essentially, this application of ultrasound allows us to visualize blood flow patterns. The Power Doppler feature allows us to evaluate a smaller area with greater intensity. In Merlyn's case the prostate exhibited a relative paucity or scarcity of vascularity or hypervascularity consistent with a lack of abnormal blood flow. Nonetheless, a less than dominant blood flow pattern was identified within millimeters of the hypoechoic lesion and remained of some concern. A lack of significant blood flow is suggestive that a cancerous process may be less than aggressive. Subsequently, an MRI scan with Spectroscopy was performed using a 3.0 Tesla magnet, confirming a region of interest in the left peripheral zone of the prostate laterally. The right side of the prostate noted decreased signal intensity as well, consistent with an unhealthy prostate (Prostatitis) but not as significant as the region of interest on the left side. The capsule of the prostate was noted to be intact without evidence of breach while the Seminal Vesicles were free of disease involvement. Spectroscopy, an integral sequence in the MRI scan (according to some experts) allows us the ability to evaluate the spectra of by-products or metabolites of cell function. In Merlyn's case his Choline + Creatine ÷ Citrate ratio was 1.77. Any value greater than 1.0 is suspicious for and therefore consistent with prostate cancer.

Based upon what we know thus far, the risk factors for prostate cancer in this patient include age, family history, PSA total and velocity, digital rectal exam findings, non-bacterial prostatitis, ultrasound imaging and MRI-Spectroscopy findings. In effect,

a multi-parametric approach has convinced me that prostate cancer was present. Given the fact that a tissue diagnosis for prostate cancer is the accepted standard of care consideration was given to a targeted biopsy while protecting against needle tracking. To state more clearly, unlike a biopsy performed elsewhere, a biopsy performed at the Diagnostic Center for Disease is one of precision. The MRI scan is expected to provide a road map identifying the target in question. Without a road map, random biopsies provide a hit or miss approach to finding a cancer. Unlike a targeted biopsy that is focused on a particular area in the prostate, a random biopsy procedure must sample all areas of the prostate in quest for the disease. The targeted biopsy is associated with a maximum of 6 defined needle punctures while a random biopsy may include upwards of 20 or more needle punctures routinely. With every needle placed the risk of complication increases. Sepsis, accompanied by fever, chills and rigors requiring hospitalization, bleeding from the Intestinal tract, Urethra and Seminal Vesicles, often times requiring a blood transfusion; pain, impotency and transient incontinence are a few of the side effects that a patient must understand, accept and be willing to endure until the healing process is complete. While the differences between targeted biopsy and random biopsies appear quite clear, there remains the issue of 'needle tracking'. When cancer cells are encountered during a biopsy protocol, cancer cells will also follow the path of the needle. Once cancer cells have escaped the prostate the stage of cancer potentially changes dramatically. To be sure, an organ confined event now becomes a non-organ confined event. **The threat of metastases that may take 10 years or longer to become evident is nonetheless, a very real possibility. Remember, 40-60% of men fail to be cured by 7-10 years (post treatment). The reason could be needle tracking, the dissemination of cancer cells when the prostate is removed or from capsular disruption from**

the placement of Radiation seeds. In an attempt to prevent the cells that escape from proliferating, we incorporate an anti-androgen prior to the biopsy and continue for two weeks post biopsy. The theory is that an all important receptor on the prostate cancer cell nucleus is blocked from accepting the male hormone Testosterone. This process weakens and/or disables the cell hastening apoptosis or cell death. The clinical validation of this event is commonly seen with a drop in PSA; tantamount to a decrease in disease activity.

Merlyn's targeted biopsy revealed the presence of prostate cancer cells associated with a Gleason score of 7 (3+4) located at the left Apico-mid prostate, consistent with the site outlined so vividly by the MRI scan. Using the diagnostic protocol, the disease process (cancer) had been confirmed, while the spread of cancer cells was discouraged, if not eliminated by the Casodex. Based upon the limited disease, this patient has a unique opportunity to treat the lesion in question focally with HIFU, while preserving the remainder of the prostate. The advantage to the patient is that a selective focal treatment modality allows the patient to resume all male related function with limited to no morbidity or collateral consequence. While there is always a risk the disease could develop at a different location, even years later, there is historical data that supports the benefit of various cell specific mechanisms of action associated with the Chronic Disease Management protocol to improve the likelihood this will not take place. As with all individuals with a diagnosis of cancer, routine surveillance testing will continue on a regular basis.

The Battle Lines are Being Drawn

According to the American Cancer Society, a new case of prostate cancer is diagnosed every 3 minutes with a biopsy

while men in their 60s, represent the most common decade of presentation and frequency of biopsy. According to the SEER (Surveillance, Epidemiologic, and End-Results) data, as "baby boomers" continue to age, the rate of prostate cancer detection is expected to worsen over the next 20 years increasing the number of men diagnosed to more than 500,000 per year. This fact suggests that we need to get the biopsy conundrum understood and solved sooner than later with a consensus opinion on how best to diagnose the number one health risk that men face.

The argument for performing a biopsy has become contentious. When, how, why and for whom a biopsy should be performed are questions that must always be addressed. **No one wants to miss a cancer anymore than one wants to find a cancer of little consequence. Noting that biopsies suffer from sampling bias, are traumatic and costly, anger cancer cells to become more aggressive and cause needle tracking, should give us reason for concern and reason to pause. Unfortunately, when cancer is found, a cascade of events occurs that may result in doing more for the disease than is required. This suggests that the landscape of prostate biopsy must change, allowing men with minimal risk to avoid the experience while scanning patients preferentially with significant risk factors in preparation for targeted biopsies, while protecting from needle tracking.** No longer are patients going to sit back, keep quiet and consent to whatever a doctor prescribes. Increasingly, patients seem to be getting the message that the person in control is the person who still has a prostate. Once your prostate is gone your options for disease control and management change drastically. Because prostate biopsy has an inherent risk of morbidity and for advancing a stage of cancer from organ-confined to extracapsular (non-organ confined), the best strategy should always be to defer a biopsy in favor of more conservative measures like treating prostatitis,

preferentially, whenever possible. This is advice you can live with while allowing you to live a better quality of life with your prostate disease under control and intact. **The decision to treat prostate cancer without a biopsy is not far-fetched when the treatment is HIFU, a treatment for benign uterine fibroids in women. I don't think men will sit back and tolerate a 'double standard' any more than women would.**

What's the future of prostate biopsy?

Hopefully, this discussion will enable more physicians to realize the diagnostic landscape needs to change. The patient can no longer be asked to assume all risks associated with a biopsy procedure where an educated guess prompts an action based on a less than specific PSA result. No longer can Urologists deny that 'needle tracking' takes place or that; biopsy procedures are potentially harmful. It may well be the evidence uncovered thus far, represents the tip of the "iceberg"; giving new meaning to why so many patients fail to be cured, despite our best technical skill. **One thing is for certain, once the biopsy process begins, I generally don't see a lot of good things that follow. Whether it relates to the disease, the biopsy procedure, the PSA that prompted the biopsy or the treatment rendered, there are few patients who are enthusiastic about the process.** If an opportunity to prevent a disease were presented as an alternative to a future biopsy, by a philanthropic group or an invested insurance carrier, I don't think it would be difficult to recruit men to study.

The biopsy associated with a tissue diagnosis will always be the standard by which other diagnostic modalities are judged. Nonetheless, when suspicion for cancer is generated by any biologic or clinical marker, imaging must become the next best test to perform, while reserving biopsy (if ever) for

those individuals whose scan is positive. While treatment of prostatitis would be an inexpensive alternative that will spare a significant percentage of men, those that are biopsied should have this procedure performed based on a map created by imaging not a biopsy needle. **Remembering that you can't hit what you can't see, must allow us to transition to a 3.0 T MRI imaging model.** Targeted biopsies can then be carried out in a region of interest to confirm a suspected cancer. While using an imaging scan to create the target that guides the biopsy needle, the number of biopsies performed per patient will decrease. Additionally, the candidates for biopsy will likely increase as the population continues to age. One would hope that Urologists will be encouraged to be more proactive educationally and less aggressive regarding who qualifies for a biopsy and who does not. **Clearly, a less than complete understanding of the facts will no longer be an allowable defense for ignorance.**