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**NEWSLETTER**

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**◆ Prostate Screening 'Wrongfully Convicted': a Reanalysis ◆**

As the US Preventive Services Task Force (USPSTF) ponders updating its controversial prostate screening recommendations, new evidence gives further support to the idea that the recommendations were ill-advised in the first place. A reanalysis of the study that strongly influenced the USPSTF recommendations — the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, has raised more doubt about the trial and its fundamental conclusions.

Prostate screening was "wrongfully convicted" on the basis of results of the PLCO trial, Jonathan E. Shoag, MD, New York Presbyterian Hospital, told *Medscape Medical News*. He hopes his findings, published May 5 in the *New England Journal of Medicine*, will cause policy makers to revise their recommendations on PSA screening and encourage the use of smarter screening and diagnostics strategies.

Initial results from the PLCO trial showed no mortality benefit for men who received PSA screening in comparison with those who did not. The trial strongly influenced the USPSTF's current recommendation against PSA screening for prostate cancer. Subsequent reanalyses of the data have revealed that many men in the control arm of the PLCO trial had received PSA testing, which might explain why their mortality rates were the same as the "screened group."

The new findings come from a follow-up survey, the Health Status Questionnaire (HSQ), that was administered to a subgroup of men in the PLCO study ten times between 1997 and 2010. In total, 4,239 control patients were surveyed with the HSQ. They were asked whether they had ever undergone PSA screening and, if so, when and why. The original study report only counted control patients as having been previously screened if they had received a PSA test in the past year, but the HSQ asked about screening in the previous 2 or 3 years and earlier. **(Continued on page 9)**

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◆ FROM THE EDITOR ◆

◆ **SPEAKER'S REMARKS - FEBRUARY 4, 2016** ◆

Our May program featured a presentation by Dr. Philip M. Arlen, Medical Oncologist, National Cancer Institute, whose topic was "**Prostate Cancer: An Overview and Update of Novel Treatment Modalities**". A summary of his remarks begins on page 11.

◆ **MEETING SCHEDULE FOR AUGUST 4, 2016** ◆

Our speaker for Thursday, August 4, 2016, is Dr. William Lloyd Glover, Jr., a urologist in private practice. His medical degree is from the University of Tennessee Health Sciences Center; his internship was at Walter Reed Army Medical Center, and his urology residency was at George Washington University Hospital. Dr. Glover served in the U. S. Army with Special Forces units. His topic is "**A Urologist is Diagnosed with Prostate Cancer. Now What?**" Hear how a urologist deals with the same challenges that newly diagnosed men face.

Please join us at 7:00 PM in the America Building (Bldg 19), 2nd floor, Room 2525. Remember, your family and friends are also welcome.

(The presentation also may be viewed via video teleconference at the Fort Belvoir Community Hospital. Go to the Oaks Pavilion, 1st floor, Room 332, to participate.)

**SEE THE BACK PAGE OF THIS NEWSLETTER FOR IMPORTANT INFORMATION ABOUT THIS MEETING.**

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## ◆ PROSTATE-SPECIFIC ISSUES ◆

**Racial and Ethnic Variation in Time to Prostate Biopsy after an Elevated Screening Level of PSA.** The study examined the racial and ethnic variation in time to prostate biopsy after an elevated screening level prostate-specific antigen (PSA).

Male members of the Kaiser Permanente of Southern California health plan, 45 years of age or older, with no history of prostate cancer or a prostate biopsy and at least one elevated screening level of serum PSA between January 1, 1998, and December 31, 2007, were retrospectively identified. All participants (59,506) were passively followed via electronic health records until their time of prostate biopsy, death, membership disenrollment or study conclusion (December 31, 2014), whichever was the initial event.

Median time until biopsy was 0.6 years (214 days) with approximately 41% of participants receiving a prostate biopsy within the study period. Results from the fully-adjusted analysis indicated that the non-Hispanic Asian or Pacific Islanders and the non-Hispanic blacks had a slightly shorter time to prostate biopsy after an elevated screening level of serum PSA compared to the non-Hispanic whites.

These data suggest, within an integrated health care organization, minimal differences exist between racial and ethnic sub-groups in their time to prostate biopsy after an elevated screening level of serum PSA. (Source: *Urology*, June 14, 2016)

**Vessel-Sparing Radiation Successfully Treats Prostate Cancer, Maintains Quality of Life:** The prostate is a tiny organ surrounded by critical vessels controlling sexual and urinary functions. If radiation therapy delivers dose to any surrounding structures, erectile dysfunction and bladder and renal irritation can result. Vessel-sparing radiation and an improved understanding of the anatomy of the prostate can reduce sexual dysfunction.

McLaughlin, et al., University of Michigan Medical School, Ann Arbor, MI, state that "they always have to keep cure as our first priority, but quality of life is a major secondary concern for men with prostate cancer. In the past cure came at a steep price in lost quality of life, but with modern refinements, it is increasingly possible to meet the new standard of successful prostate cancer treatment: that is, cure with quality of life." In a review in *Lancet Oncology*, the authors describe the importance of functional anatomy in determining plans of treatment with radiation oncologists that can spare critical urinary and sexual structures. Functional anatomy can vary from patient to patient.

MRIs can enable radiation oncologists to administer vessel-sparing radiation by showing the distinct functional anatomy of a patient. In addition, MRIs can inform the best treatment options. For example, if the tumor is outside the prostate gland, then radiation therapy should be administered after surgery.

Vessel-sparing radiation would require physicians to train in MRI anatomy so that they could properly identify key structures. "The benefit of the functional anatomy approach goes well beyond improving sexual function. It has improved urinary and rectal function as well," explained McLaughlin.

Vessel-sparing radiation can preserve sexual function in 90% of men at the 5-year follow-up while achieving excellent rates of successful treatment of aggressive disease. MRIs can play an integral role in guiding not only vessel-sparing but also overall treatment approaches.

"For patients who appear to have slow-growing, non-aggressive cancers, MRI can confirm there is no aggressive cancer present. For such patients, surveillance is an excellent choice. By avoiding treatment altogether when appropriate, all the side effects and quality of life impact from treatment is avoided," said McLaughlin.

"On the other end of the spectrum, MRI may actually reveal more serious cancers not sampled by the biopsy. This can shift treatment to a more aggressive approach necessary to cure such cancers," he added. Source: *Lancet Oncology*, May 27, 2016)

**Expectant Management for PCa More Likely at Academic Centers.** New findings suggest that men with low-risk prostate cancer (PCa) are more likely to receive expectant management (EM) for their disease if they are evaluated at academic rather than community centers. Odds of using this strategy are 2.7-fold greater versus community facilities.

Using the National Cancer Data Base (NCDB), Lester-Coll, et al, Yale University School of Medicine, performed a retrospective analysis of 2010-2013 data on 91,556 men with low-risk PCa. Of these, 39,139 were evaluated at academic centers and 52,417 were evaluated at community facilities. In all, 10,880 received EM (active surveillance/watchful waiting) and 80,676 received treatment.

The researchers reported that a significantly higher proportion of men evaluated at academic facilities received EM (17% vs. 8%). After statistical adjustments, patients evaluated at an academic versus community facility had 2.7 times increased odds of being placed on EM.

The researchers offer a possible explanation for greater EM use at academic centers in that men with low-risk PCa may be referred to these centers because of greater medical complexity and burden of comorbidity illness, and thus may be less amenable to definitive treatment. They pointed out, however, that their study found no significant differences in comorbidity scores between patients evaluated at academic and community centers. Therefore, their results do not support the hypothesis that differences in patient-level comorbidity between community and academic centers are responsible for the observed differences in EM use.

The researchers suggest that immeasurable patient characteristics are another possibility. For example, patients who seek opinions at academic centers may be more motivated to obtain multiple opinions and/or are more hesitant to pursue treatment.

It is also possible that physicians in academic practices are more shielded or less concerned with the difference in reimbursement of EM and definitive treatment because academic salaries are less directly dependent on clinical revenue. Therefore, the pressure to treat patients may be reduced in academic practice.

With respect to study limitations, the researchers pointed out that the NCDB does not differentiate between active surveillance and watchful waiting. In addition, 3,398 men were coded ambiguously as have received “no treatment” and excluded from the study. The investigators also noted that the NCDB does not provide certain important details of individual patient records, so it is possible that differences in patient characteristics such as functional disability or performance status are not adequately measured, leading to selection bias. (Source: Renal and Urology News, July 8, 2016)

**Robotic Surgery Reduces Blood Loss and Length of Stay in Obese Men With Prostate Cancer.** Length of stay and blood loss were reduced with robotic-assisted radical prostatectomy (RARP) compared with open radical prostatectomy in obese men with prostate cancer who underwent surgery for their disease.

Prostate cancer is the most common solid organ malignancy in men in the United States; 1 in 6 men will develop the disease during their lifetime. A frequently chosen treatment options is radical prostatectomy, which involves removing some surrounding tissue as well as the prostate gland, performed either as robotic-assisted or as an open procedure.

Almost 40% of adults in the United States are obese. Obesity often comes with comorbidities that make operations challenging, such as diabetes, heart disease, and obstructive sleep apnea.

Gupta, et al, Department of Urology, Loyola University's Stritch School of Medicine, Chicago, identified 9,108 obese men who underwent radical prostatectomy; 60.4% of whom underwent RARP, and 39.6% underwent open prostatectomy. Compared with patients who underwent open prostatectomy, the patients who underwent RARP were 83% less likely to require blood transfusions and 72% less likely to require prolonged hospital stays. Risk of infections and other complications, however, were not reduced by the robotic-assisted surgery.

Given that the complication rates are similar between the robotic and open surgery options, the implication for urologists is that both techniques remain interchangeable. The approach chosen should be dictated by the surgeon's comfort level. For obese patients with prostate cancer, the findings suggest that both approaches to the surgery are feasible and safe. (Source: *Current Urology*, 2015;8(3):156-161, via Oncology Nurse Advisor, June 3, 2016)

**Erectile Dysfunction Predicts Higher Risk of Osteoporosis.** ED can be considered an early predictor of osteoporosis. Men with a history of erectile dysfunction (ED) are at higher risk of osteoporosis, according to a new study.

Chih-Lung Lin, et al, Kaohsiung Medical University, Taiwan, compared 4460 men aged 40 years or older diagnosed with ED from 1996 to 2010 with 17,480 randomly selected age-matched patients without ED. During follow-up, osteoporosis developed in 264 patients with ED (5.92%) and 651 without ED (3.65%). The overall incidence of osteoporosis was 3-fold higher in the ED group than the non-ED group (9.74 vs. 2.47) per 1000

person-years. Osteoporosis was 3 times more likely to develop in men with ED compared with those who did not have ED.

The risk varied by age. ED patients aged 40 to 59 years had a 3.6 times increased risk of osteoporosis and those aged 60 years and older had a 3.5 times increased risk compared with the non-ED group. Because of the easy and noninvasive evaluation of osteoporosis, patients with ED should be examined for bone mineral density, and men with osteoporosis should be evaluated for ED, the investigators said.

Dr. Lin and colleagues discussed possible mechanisms underlying the relationship between ED and osteoporosis. For example, men with ED have lower naturally-available free testosterone than those without ED, they noted, adding that androgens may have a key role in regulating bone formation in men. In addition, men with low testosterone have a marked increase in the risk of fragility fractures. Androgen deprivation therapy and orchiectomy have been associated with an increased risk of osteoporosis and fractures. "Therefore, testosterone depletion might increase the risk of osteoporosis," the investigators concluded. (Source: *Medicine* (2016;95:p e4024) via Renal and Urology News, July 11, 2016)

**ADT Plus Radiation Improves Survival in Metastatic Prostate Cancer.** For men with metastatic prostate cancer (mPCa), overall survival (OS) is improved for those treated with androgen deprivation therapy (ADT) and prostate radiotherapy (RT), compared with ADT alone, according to a study published online in the *Journal of Clinical Oncology*.

Rusthoven, et al, University of Colorado School of Medicine, examined the overall survival of men with mPCa treated with ADT, with and without prostate RT. A total of 6382 men with mPCa were identified, of whom 8.4% received prostate RT. At a median follow-up of 5.1 years, the researchers found that the addition of prostate RT to ADT correlated with improved overall survival. In this large contemporary analysis, men with mPCa receiving prostate RT and ADT lived substantially longer than men treated with ADT alone, the authors concluded. (Source: *Healthday News*, via Renal And Urology News, June 29, 2016)

**The Role of PSA in Detection and Management of Prostate Cancer.** The prostate specific antigen (PSA) test clearly provides the opportunity for clinically relevant prostate cancer to be detected at a stage when treatment options are greater and outcomes may be improved. However, in some patients, the PSA test may lead to investigations which can identify clinically insignificant cancers which would not have become evident in a man's lifetime. In addition, a raised PSA may often indicate benign prostatic enlargement, and this may provide an opportunity for treatment of this condition before complications develop. The lack of sensitivity and specificity that characterizes PSA testing in the initial diagnosis of prostate cancer largely disappears after treatment of localized prostate cancer, especially after surgery. Three monthly PSA measurement is usually recommended for the first year after primary treatment. Subsequently less frequent testing is required. A PSA rise after primary treatment usually indicates biochemical recurrence and often the need for further therapy. There are two promising urinary RNA biomarkers, prostate cancer antigen 3 (PCA3) and fusion gene TMPRSS2:ERG,

both of which aim to distinguish between men with low-risk (indolent) and those with aggressive (clinically significant) cancers. (Source: *The Practitioner*. 2016 Apr [Epub], via Uro Today, June 28, 2016)

**Medical Hospitalizations in Prostate Cancer Survivors.** A recent study explored the context and reasons for medical hospitalizations among prostate cancer survivors and their relationship with obesity and the type of prostate cancer treatment.

A retrospective review of medical records was performed at an academic institution for male patients aged 40 years and older who were diagnosed and/or treated for prostate cancer 2 years prior to the study's observation period. Statistical techniques were used to compare patients' characteristics, admission types, and medical comorbidities by body mass index (BMI) and prostate cancer treatment. Mean age for the study population was 76 years. Two hundred and forty-five prostate cancer survivors were stratified into two groups: non-obese (BMI < 30) and obese (BMI ≥ 30). The study population's characteristics analyzed by BMI were similar including Gleason score, presence of metastatic disease and genitourinary-related side effects.

Only 13 % of admissions were for complaints related to their genitourinary system. Neither the specific treatment that the patients had received for their prostate cancer, nor obesity was associated with the reasons for their medical admission.

Survivorship after having a diagnosis of prostate cancer is often lengthy, and these men are at risk of being hospitalized, as they get older. From this inquiry, however, it has become clear that neither body mass index nor prior therapy is associated with specific admission characteristics, and only a minority of such admissions was directly related to prostate cancer or the genitourinary tract. (Source: *Medical Oncology* (Northwood, London, England), June 20, 2016 [Epub], via Uro Today, June 28, 2016)

**Is it Time to Abandon the Digital Rectal Examination?** In 2012 the US Preventive Services Task Force released recommendations against prostate specific antigen (PSA) based screening for prostate cancer, but did not fully address screening via digital rectal exam (DRE). Many practitioners continue to perform DRE in attempts to identify men with clinically significant prostate cancer (CSPC). A recent study sought to determine the value of DRE in detecting CSPC in the era of PSA-based screening.

Data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial, a nationwide population-based study evaluating cancer screening programs and their impact on cancer mortality, was analyzed for PSA, DRE, and cancer status. In the screening arm of the PLCO, 38,340 men received annual PSA and DRE examinations for the first three years. Those with an abnormal test result were referred for biopsy.

The ability of DRE to detect CSPC, defined as intermediate risk or higher based on National Comprehensive Cancer Network guidelines and age ≤ 75, was evaluated in the context of both normal and abnormal PSA. 5,064 men had abnormal DRE in the setting of normal PSA, of which 99 (2%) were diagnosed with CSPC. When both PSA and DRE were abnormal, 218 (20%) participants were diagnosed with CSPC (RR = 2.06 [1.78-2.39] versus abnormal PSA alone).

DRE screening in the setting of normal PSA captured an additional 2% of men with CSPC. This incremental gain suggests that routine DRE screening subjects a large number of men to invasive, potentially uncomfortable examinations for relatively minimal gain.

Key Limitations: Our conclusions are based on data derived from the PLCO study which has been criticized on the basis of inconsistent biopsies following positive screening tests, lack of end of study biopsies to determine population disease burden, and low numbers of black men. (*Current Medical Research and Opinion*, June 4, 2016, [Epub ahead of print])

**Is "Active Surveillance" an Acceptable Alternative?: A Qualitative Study of Couples' Decision Making about Early-Stage, Localized Prostate Cancer.** The objective of the study was to describe decision-making by men and their partners regarding active surveillance (AS) or treatment for early-stage, localized prostate cancer. Fifteen couples were recruited from a cancer center multispecialty clinic, which gave full information about all options, including AS. Data were collected via individual, semi-structured telephone interviews.

Most patients were white, non-Hispanic, had private insurance, had completed at least some college, and were aged 49-72 years. Ten chose AS. All partners were female, and couples reported strong marital satisfaction and cohesion. All couples described similar sequences of a highly emotional initial reaction and desire to be rid of the cancer, information seeking, and decision making.

The choice of AS was built on a nuanced evaluation of the man's condition in which the couple differentiated prostate cancer from other cancers and early stage from later stages; wanted to avoid/delay side effects, and trusted the AS protocol to identify negative changes in time for successful treatment. Treated couples continued to want immediate treatment to remove the cancer.

The researchers concluded that having a partner's support for AS may help a man feel more comfortable with choosing and adhering to AS. Using decision aids that address both a man's and his partner's concerns regarding AS may increase its acceptability. Our research shows that some patients want to and do involve their partners in the decision-making process.

Ethical issues are related to the tension between desire for partner involvement and the importance of the patient as autonomous decision-maker. The extended period of decision making, particularly for AS, is also an ethical issue that requires additional support for patients and couples in the making of fully informed choices that includes AS. . (Source:

Narrative Inquiry in Bioethics, 2016, via UroToday, July 20, 2016 [ Epub])

**Surgical Procedure Improves Survival Rates for Men with Prostate Cancer if Radiation Treatments Fail.** Approximately 14 percent of men will be diagnosed with prostate cancer at some point in their lifetimes, according to the National Institutes of Health. Radiation therapy traditionally has been a primary treatment for the cancer, but

one-fourth of men have a recurrence of prostate cancer within five years after the therapy. Now, a University of Missouri School of Medicine researcher has found that a complex procedure to remove the prostate achieves excellent long-term survival for men after radiation therapy has failed.

Pokala, MD, et al, Division of Urology, University of Missouri School of Medicine, note that prostate cancer is a common cancer, and more than 27,000 men are estimated to have died from the disease in 2015. By studying a national database of prostate cancer cases, the researchers found that a procedure known as salvage radical prostatectomy can greatly increase a man's chance of survival when traditional radiation therapy has failed to eradicate the cancer.

Using the Surveillance, Epidemiology and End Results (SEER) program database, Pokala and his research team studied 364 patients who underwent a salvage radical prostatectomy surgery after unsuccessful radiation treatments. Looking at survival rates, the researchers found that 88.6 percent of men were still alive 10 years later and 72.7 percent of men were still alive 20 years later.

During a salvage radical prostatectomy, the prostate gland and surrounding tissue are surgically removed to keep the cancer from spreading. The procedure is challenging because tissue that surrounds the prostate is scarred during radiation treatment, making it difficult for the surgeon to identify and cut out tissue that needs to be removed. If the cancer is localized, a highly skilled surgeon can remove the gland and surrounding tissue using a robotic minimally invasive technique or through an open surgery.

"Because radical prostatectomy is a complex surgery, there can be a reluctance to undergo the procedure," Pokala said. "However, this study shows that it is a viable treatment option. This can bring a renewed hope and peace of mind to men living with prostate cancer."

The study, "Survival Outcomes in Men Undergoing Radical Prostatectomy after Primary Radiation Treatment for Adenocarcinoma of the Prostate," recently was published by *Clinical Genitourinary Cancer*, a peer-reviewed journal on the detection, diagnosis, prevention and treatment of genitourinary cancers. (Source: Missouri Medicine Edu News, March 10, 2016)

### **(PSA SCREENING - CONTINUED FROM PAGE 1)**

"Overall, the proportion of control participants who reported having undergone at least one PSA test before or during the trial was close to 90%," Dr Shoag reported. Furthermore, when participants from the intervention arm were surveyed with the same HSQ, men in the control group reported having had more cumulative PSA testing than men in the intervention group.

"These clarifications should be considered by policymakers and payers debating reimbursement and meaningful use of PSA testing, particularly given the mounting evidence that intermittent PSA testing decreases the costs and harms of screening while preserving the benefits of annual testing," noted Dr Shoag.

"The USPSTF recommendation against PSA screening has resulted in rapid declines in PSA screening nationally," he added. "As a result, we're diagnosing fewer prostate cancers, and perhaps most concerning, physicians may be under the mistaken impression that there is no value to prostate cancer screening. The remaining data, including the large, randomized ERSPC trial [ *N Engl J Med.* 2009 Mar 26;360:1320-8], demonstrate that PSA screening prevents men from dying of prostate cancer," he added.

"This helps to put the negative results of the PLCO study in perspective," Stacy Loeb, MD, from New York University, told *Medscape Medical News*. "If virtually all men in the control group got screened, it is no surprise that the rates of prostate cancer death were similar to the screening arm."

But Gerald L. Andriole, MD, the lead author of the PLCO trial, told *Medscape Medical News* that Dr Shoag's data "are not new or substantially different" from what has been reported by others, including the PLCO statisticians themselves ( *Clin Trials.* 2010 Aug;7:303-11). "Notwithstanding the PLCO results, it seems that, based on ERSPC results alone, the USPSTF task force seemed to believe that the relatively modest mortality benefit was not enough to justify the human costs of screening," said Dr Andriole, Washington University School of Medicine, St. Louis, MO. He noted that new data regarding screening are due out soon — the PROTECT trial from the UK. Those are the data that should matter much more

Dr. Shoag responded that Dr Andriole was correct that some of the HSQ data were included in a prior low-visibility paper, but in a complex manner in the body of the manuscript and not in the abstract. "We therefore believed that even though a portion of these data was in theory available, given the widespread misunderstanding of this information and the immediate policy implications, it was imperative that these data be clarified promptly and prominently," he added. (Source: American Urological Association (AUA) 2016 Annual Meeting: LBA-02, abstract 1140, presented May 9, 2016, via *Medscape Medical News*, May 11, 2016)

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# PROSTATE CANCER OVERVIEW AND UPDATE OF NOVEL TREATMENT MODALITIES

(A summary of a presentation to the WRNMMC Prostate Cancer Support Group, May 7, 2016)

by

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**Attending Physician, Genitourinary Malignancies Branch, National Cancer Institute, Bethesda, Maryland**

## Introduction

Thank you for the opportunity to be with you this evening to discuss the exciting changes in the treatment of prostate cancer. There are so many emerging therapies that it is difficult for even the experienced practitioner to remain abreast of developments!

## Overview

While 200,000 new prostate cancer diagnoses are made in the USA each year, after initial treatments (for example, post-surgery), only about 15,000 men still have cancer needing ongoing therapy. Most of this presentation, especially the latter part, focuses on options and considerations for those men.

## Localized Prostate Cancer

Prior to 1998, conventional recommendations for treating prostate cancer included surgery (e.g., total prostatectomy) or irradiation of the prostate -- accompanied by prompt use of androgenic hormone deprivation or chemotherapy – based on post-treatment rising PSA values or symptom-driven imaging indicative of recurrence or local or distant expansion/metastases. In general, the higher the Gleason score and/or the higher the PSA levels, the more frequently the urologist-oncologist advised initial radiation therapy rather than initial prostatectomy. With various other existing commonly employed approaches (hormone deprivation, chemotherapy), palliation was seen as the last therapeutic resort.

After one of the more decisive treatments, a rise in PSA would then prompt imaging studies before commencing any subsequent adjunctive therapy for presumptive metastatic prostate cancer.

## Watchful Waiting

There has been a reduction in the sense of immediate fear and desperation with wider recognition by patients that the natural history of many relatively non-aggressive prostate cancers provides an extended period of years or decades with relatively slowly progressive disease. The concept of “watchful waiting” is accepted more comfortably as an option in an era when non-invasive techniques can monitor the cancer’s presence and location(s).

Previously, therapeutic decisions were powerfully influenced by the circulating blood PSA level, the prostatic biopsy Gleason score, and findings from staging. Nowadays, the assessment of risks by the patient, family and clinician regarding quality of life are taken into account.

By the late 1990s, clinicians and patients increasingly discussed the role for other factors affecting when and how aggressively to treat prostate cancer. "Watchful waiting" was introduced as a consideration. It reflected recognition that, although prostate cancer was, or remained present after applied treatment modalities, perhaps its natural history and the quality of life of the patient would be adversely impacted by commencement of further aggressive therapies.

Unlike other cancers, some adjuvant therapies for slowly advancing or seemingly static prostate cancer may have a detrimental effect on the patient's sense of well-being and quality of life. In contrast, some men are troubled by their persistent awareness of a high PSA and are not comfortable with a "wait and see" approach. Indications of likely expanding or metastatic disease encouraged the use of chemotherapy or chemical or anatomic castration.

### **Doubling Time**

Even the first PSA at the time of diagnosis may be important. If, for example, a prostate-resected or prostate-irradiated patient has a rising PSA ("biochemical recurrence") the "doubling time" from the post-treatment baseline value can now be a component in the algorithm for decisions. Different approaches are advised if the PSA doubling time is as short as three months compared to 4-14 months, or fifteen or more months (so-called indolent-growth cancer).

This "PSA doubling time" assessment was an important marker to follow after a decisive, invasive treatment (e.g., prostatectomy or irradiation). PSA doubling time now serves to monitor the effect of one or more courses of intermittent (hormone) androgen deprivation therapy. The use of Goserelin®, as an example of a targeted anti-androgen receptor, "sets back the PSA clock" and the doubling time reassessed from that point.

The interpretation of a PSA result from a blood draw on any specific day must take into account the variation that can occur from day-to-day. It may have wider swings for one man than another. Thus, it is trends or the average of several results that may be more reflective of post-treatment regression or progression-associated increases. (In response to the question, "Is something better than PSA coming along?" Dr. Arden doesn't anticipate a replacement or an improved PSA test in the near term.)

### **Hormone Approaches/Androgen Deprivation Therapies**

Genetic engineering has enabled molecules to target specific prostate cell androgen receptors and to suppress growing prostate cells more than other androgen-responsive body cells. These methods are reducing the use of chemotherapy agents that – although widely appreciated for other cancer and leukemia treatment advances – are usually too non-specific in this new era. However, it must be recognized that hormone therapies are not

without some consequences – including muscle wasting, hot flashes (“male menopause-like”), or depression.

Androgen deprivation therapy continues to evolve. It will lower testosterone (and PSA) for most treated men, but there may be a surge (“flare”) in testosterone shortly after cessation of a course of therapy. Clinical trials continue to explore whether intermittent ADT is preferable to continuous ADT – or whether, indeed, sequential therapy with different androgen receptor blocking hormones are advisable. Indeed, recent studies have shown unexpectedly good benefits of treating, for example with Enzolutamide® before chemotherapy.

In addition to existing and emerging (designer) hormone therapies, there are medications that have hormonal effects. For example, the well-known antifungal agent, ketoconazole, prompted chemists to design and test Aparatidone (Zykeda®). But, of course, there are always cautions. The genetics of liver metabolism of Aparatidone can be a problem for some men.

An advance in radiotherapy -- beyond the “seed” implants used to place radiation close to multiplying prostate cancer cells – is the recent use of a Radium 223-based treatment agent (Xofigo®) being studied for symptomatic and metastatic prostate cancer in the “ALSYMPCA” trial.

### **What Else is New on the Horizon? Immuno-oncology!**

The remarkable advances in the past two decades of cancer therapy using immune attack (mostly monoclonal antibody) molecules to find and impair cancers -- especially by damaging their rapidly growing blood vessels that support the cancer – has led to name recognition of some medicines like Gleevec®.

Immune-based therapies, including experimental vaccines, begin by targeting abnormal or excessive molecules produced by, and found on, prostate cells selectively. The previous clinical reluctance to use very toxic chemotherapy (to damage the rapidly growing cancer cells) is giving way to other approaches such as Immuno-Oncology – but mostly still in conjunction with other known therapeutic modalities.

### **Monoclonal Antibodies: Circulating Immune Fighter Molecules**

Monoclonal antibodies are very, very specific antibodies. They are made through genetic engineering and are produced in sterile production laboratories such that every molecule is like every other such immune molecules. They can be used in either direct or indirect approaches to targeted cells. For example, they could be linked to a toxic radioactive element. Once the antibody has found its target cell, it attaches and the radioactivity is brought directly against the target (cancer) cell. Such monoclonal anti-prostate antibodies are now also being explored for whether they can alter cancer cells to enable an otherwise restrained immune system to have the “brakes released” and enable the otherwise restrained, confused immune system of the patient to clearly see and attack the cancer. This approach is based on “check-point inhibitors” concepts.

### **Vaccines**

There are specific vaccines, like Provenge® that have demonstrated that successive series of treatment may work. Provenge® immunizes so as to create a target out of the prostate's prostatic acid phosphatase.

An alternative approach, the vaccine ProsVAC®, developed at NCI, has improved survival substantially in some trial participants. ProsVAC® is based on the concept that the human immune system will develop antibodies and use white cells of various types to attack a “foreign intruder” detected as “non-self” by its chemical structure. To get a man's body to attack PSA and the PSA-generating prostate tissue – especially expanding cancer – cells, there are various ways to immunize. The ProsVac® takes the genetic blueprint of DNA that will be processed into an foreign protein once it is injected inside the body. Getting this PSA-variant gene in can be accomplished by using a distant cousin virus of smallpox vaccine – fowlpox -- that has no risk of smallpox-like disease in humans – even immunosuppressed or ill patients.

Once the virus carrying the gene into the body has educated the immune system to attack the “foreign” PSA variant protein, it encounters the normal PSA being produced in large amounts by the prostate cancer cells. The immune system will attack the cancer cells. In current studies, booster immunizations of recombinant fowlpox can be given.

As yet the ideal direct comparison studies (ProsVAC® might be tested against Provenge®) hasn't occurred.

### **Combination Therapies are Key to Future Advances**

Vaccines administered in combination with other therapies (e.g., hormones as listed above) are showing greater effect than just hormonal therapy alone. Similarly, radiation may help vaccines work. Some researchers are exploring if non-immune therapies may “unmask” the prostate cancer resulting in a greater vulnerability to other established treatment approaches – even if tumor burden seems not drastically reduced immediately. Even though the prostate tumor size may not shrink substantially, experience is growing to suggest that combined approaches wound prostate cancer cells to be less able to grow and/or metastasize as they otherwise would. Anti-androgenic hormone-based attacks may be more effective in combination (vaccine or other modalities) than just hormone therapy alone would be.

### **Closing**

It has been my pleasure to be with you tonight. We should all be gratified by the progress being made in the battle against prostate cancer.

◆ WRNMMC US TOO COUNSELORS ◆ (As of August 1, 2016)

(THESE PERSONS ARE WILLING TO SHARE THEIR EXPERIENCES WITH YOU. FEEL FREE TO CALL THEM.)

**SURGERY**

|                   |                   |                |                              |
|-------------------|-------------------|----------------|------------------------------|
| Tom Assenmacher   | Kinsvale, VA      | (804) 472-3853 |                              |
| Jack Beaver       | Falls Church, VA  | (703) 533-0274 | 1998 (Open RP)               |
| Rob Calhoun       | Annapolis, MD     | (410) 293-6635 | 2011 (Robotic Surgery)       |
| Gil Cohen         | Baltimore, MD     | (410) 367-9141 |                              |
| Richard Dorwaldt  | San Antonio, TX   | (210) 310-3250 | (Robotic Surgery)            |
| Michael Gelb      | Hyattsville, MD   | (240) 475-2825 | (Robotic Surgery)            |
| Robert Gerard     | Carlisle, PA      | (717) 243-3331 |                              |
| Tony Giancola     | Washington, DC    | (202) 723-1859 | 2008 (Radical Prostatectomy) |
| Ray Glass         | Rockville, MD     | (301) 460-4208 |                              |
| Monroe Hatch      | Clifton, VA       | (703) 323-1038 |                              |
| Tom Hansen        | Bellevue, WA      | (425) 883-4808 | 1998 (Robotic Surgery)       |
| Bill Johnston     | Berryville, VA    | (540) 955-4169 |                              |
| Dennis Kern       | San Francisco, CA | (415) 876-0524 |                              |
| Sergio Nino       | Dale City, VA     | (703) 590-7452 |                              |
| Ed Postell        | Collegetown, PA   | (610) 420-6765 | (Robotic Surgery)            |
| George Savitske   | Hellertown, PA    | (703) 304-3081 | 2000 (Open RP)               |
| Artie Shelton, MD | Olney, MD         | (301) 523-4312 |                              |
| Jay Tisserand     | Carlisle, PA      | (717) 243-3950 |                              |

**PROSTATE CANCER AND SEXUAL FUNCTION**

|                 |                   |                |
|-----------------|-------------------|----------------|
| James Padgett   | Silver Spring, MD | (301) 622-0869 |
| George Savitske | Hellertown, PA    | (703) 304-3081 |

**RADIATION**

|                  |                    |                |                                |
|------------------|--------------------|----------------|--------------------------------|
| Leroy Beimel     | Glen Burnie, MD    | (410) 761-4476 | 1987 (External Beam Radiation) |
| Bob Bubel        | Grand Junction, CO | (970) 263-4974 | 2010 (Proton Beam Radiation)   |
| Harvey Kramer    | Silver Spring, MD  | (301) 585-8080 | 1998 ((Brachytherapy)          |
| Joseph Rosenberg | Kensington, MD     | (301) 495-9821 | 2009 (Brachytherapy)           |
| Barry Walrath    | McLean, VA         | (571) 969-8269 | 2001 (Brachytherapy)           |

**WATCHFUL WAITING**

|            |               |                |                     |
|------------|---------------|----------------|---------------------|
| Tom Baxter | Haymarket, VA | (703) 753-8583 | Active Surveillance |
|------------|---------------|----------------|---------------------|

**SPOUSE SUPPORT**

|                 |                   |                |
|-----------------|-------------------|----------------|
| Renate Bubel    | Fairfax, VA       | (703) 280-5765 |
| Karen Collins   | Mechanicsburg, PA | (717)-766-6464 |
| Betty Kramer    | Silver Spring, MD | (301) 585-8080 |
| Ellen Rosenberg | Kensington, MD    | (301) 495-9821 |
| Nancy Wallrath  | McLean, VA        | (703) 915-8108 |

**OTHER THERAPIES/MULTIPLE THERAPIES**

|                  |                   |                |   |
|------------------|-------------------|----------------|---|
| Howard Bubel     | Fairfax, VA       | (703) 280-5765 | 1995,1996 (Hormonal, Cryosurgery, Sex-Function) |
| Arthur E. Clough | Kerryville, TX    | (830) 896-8826 | 1993 (Surgery and Radiation)                    |
| Pete Collins     | Mechanicsburg, PA | (717) 766-6464 | 2007, 2009 (Surgery, Radiation, Hormonal)       |

◆ MEETING ANNOUNCEMENT ◆

THURSDAY, AUGUST 4, 2016

7:00 - 8:30 PM

AMERICA BUILDING (BLDG 19, 2D FLOOR) ROOM 2525  
(DIRECTLY ABOVE THE LAB/PHARMACY)

WALTER REED NATIONAL MILITARY MEDICAL CENTER

◆ SPEAKER ◆

WILLIAM LLOYD GLOVER, JR, MD

FAIRFAX UROLOGY CENTER, LTD, FAIRFAX, VA

◆ TOPIC ◆

**"A UROLOGIST IS DIAGNOSED WITH PROSTATE CANCER. NOW WHAT?"**

**Gate/Parking:** If you enter the base through South Gate (Gate 2) off Rockville Pike/Wisconsin Avenue, take the first right (Palmer Road South). On your left will be the Emergency Room. Continue to follow signs to the America Building and the America parking garage.

**Security:** A military ID card is required to get on base. Persons without a military-related ID card who are attending the meeting are required to register in advance in order to gain entry. To register, contact the CPDR front desk at 301-319-2900 at least four business days prior to Thursday, 2016, to arrange entry. Have a photo ID card ready when arriving at the gate.