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THE CENTER FOR PROSTATE DISEASE RESEARCH - AN OVERVIEW OF CLINICAL TRIALS AND TRENDS IN PROSTATE CANCER MANAGEMENT

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Walter Reed Army Medical Center

(A summary of a presentation to the WRAMC Us TOO Chapter on May 6, 2009)

INTRODUCTION

It is a pleasure to be with you again tonight. A year ago I spoke about some of the salient issues affecting the surgical management of prostate cancer. Tonight my purpose is two-fold. First, I want to present the principal activities of the Center for Prostate Disease Research (CPDR), particularly those affecting clinical practices. Then I will discuss clinical research and new developments in the management of prostate cancer.

THE CENTER FOR PROSTATE DISEASE RESEARCH (CPDR)

Most of you are familiar with the CPDR as you experience it at Ward 56, but we are part of a much larger organization. The CPDR is under the Uniformed Services University of the Health Sciences and its Department of Surgery. Our funding and many administrative functions are provided by the Henry M. Jackson Foundation. The CPDR itself is actually divided into three elements. One is the clinical research program which you experience upstairs on Ward 56. The second is our tri-service national database program and our biospecimen banking program—many of you who were treated here at WRAMC are participants in these programs. And the third is our basic science research program located in Rockville, MD.

I want to emphasize that these organizations closely interface with each other. For example, many of the specimens and serum collected from the clinical research program and the Armed Forces Institute of Pathology are sent to our basic science research program in Rockville where cutting-edge technology produces studies that combine with the Tri-Service database to evaluate and correlate clinical-pathological data with molecular findings, thereby influencing clinical practices. **(Continued on page 8)**

♦ ***INSIDE THIS ISSUE*** ♦

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♦ FROM THE EDITOR'S DESK ♦

Over the past year I have mentioned concerns about our ability to sustain the publication of this newsletter in view of its increasing popularity and the associated printing and distribution expenses. The situation is now complicated by the global economic downturn that is affecting the ability of our traditional corporate supporters to contribute to our program. Many other nonprofit organizations are facing the same dilemma. No doubt you are aware of them in your own communities.

We faced a similar situation ten years ago, and now as then, our board of directors has decided to continue the newsletter in the expectation that you, the readership, will sustain us until such time as we can regain the financial support of our major contributors. Page 3 has a more detailed explanation of our intentions to keep going. Please read it carefully and respond if you can.

♦ MAY SPEAKER'S REMARKS ♦

Our May program featured Dr. Stephen Brassell, a urologic oncologist at Walter Reed Army Medical Center and Assistant Director, CPDR, who discussed the role of the Center for Prostate Disease Research (CPDR), and brought us up-to-date about the promising developments in the diagnosis and treatment of prostate cancer. His topic was "CPDR Present and Future – An Overview of Clinical Trials and Trends in Prostate Cancer Management." A summary of the presentation begins on page 1.

♦ MEETING SCHEDULE FOR AUGUST 5, 2009 ♦

Our speaker for Wednesday, August 5, 2009, is Dr. Leslie Cooper, Ph.D., a consulting psychologist to the Center for Prostate Cancer Research and other cancer centers within WRAMC. As a member of interdisciplinary medical teams, she provides psychological-social services to cancer patients and their families as they cope with the disease. Her topic is "Why Talking is Important, or Why 'Sucking It Up' Doesn't Work." Join us in Joel Auditorium at 7:00 PM, Wednesday, August 5, 2009, as Dr. Cooper presents important issues affecting men with prostate cancer and their families. Family members and friends are always welcome.

DISCLAIMER: The materials contained in this newsletter are solely the individual opinions of the authors. They do not represent the views of any Department of Defense agencies. This newsletter is for informational purposes only, and should not be construed as providing health care recommendations for the individual reader. Consult with your physician before adopting any information contained herein for your personal health plan.

♦ AN OPEN LETTER TO THE READERSHIP ♦

Your letters, calls and emails tell us how much you appreciate receiving the WRAMC Us TOO Newsletter. The newsletter is published by the WRAMC Us TOO Prostate Cancer Support Group to keep you, your families, and friends informed about developments in the diagnosis and treatment of prostate cancer. The newsletter began in 1991 as a 10-page publication produced on a copier in 90 copies intended for distribution among men being treated for prostate cancer at WRAMC. It is now produced in 2,000 copies and distributed nationwide upon request and without charge to 2,000 readers. There are no paid employees. Instead, the newsletter is produced by volunteers within the support group. We receive much encouragement and support from the staff at WRAMC, but the expense of publishing the newsletter is the responsibility of the WRAMC Us TOO Prostate Cancer Support Group. It costs approximately $7,500 annually to produce the newsletter, and we rely on donations and corporate sponsorships to cover the expense.

The current national economic crisis has drastically affected our ability to obtain support from our traditional corporate patrons. Many of them have made major reductions in their staffs and reduced their gifts and donations to worthy causes they have long supported. At any rate, we were unable to obtain corporate support for 2009. Our board of directors considered alternatives to sustain the continued publication of the newsletter: annual subscriptions by the readers (too unwieldy); an all-electronic delivery via email (discounted because we believe the large majority of our readers prefer the newsletter in hard copy, and others may lack internet access). Accordingly, we have decided to continue our outreach for corporate support for 2010 and rely on an appeal to the readership in the meantime.

We faced a similar situation in 1999. Fortunately, we were able to continue publication without interruption thanks to a generous response from the readership that sustained us until we were able to regain corporate support. So we again solicit your understanding and support at this time. If you value the newsletter and are in a position to make a contribution, please use the form below to do so. <u>All donations will be acknowledged.</u>

WRAMC Us TOO is a non-profit educational entity organized under Section 501(c)(3) of the Internal Revenue Code. Donations to it are tax-deductible.

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Surgery Enhances Survival in Younger Men. Although the majority of all prostate cancer is diagnosed in men older than 65, its prevalence is growing among men younger than 50. In fact, about one in 10,000 men under the age of 40 will be diagnosed with prostate cancer this year.

Pokala and Menon, Henry Ford Hospital's Vattikuti Urology Institute, studied more than 8,200 men under age 50 with prostate cancer to determine which treatment option offers the best chance for long-term survival for younger prostate cancer patients. Among the study group, 73 percent were white and about 22 percent were black. The mean age was 46. Of the patients, 1,065 were managed with no definitive treatment (watchful waiting); 6,614 with radical retropubic prostatectomy; and 600 with external beam radiotherapy.

The results showed that the surgical procedure improves the 5-, 10-, 15- and 20-year survival for younger patients, when compared with other standard treatments such as radiotherapy or watchful waiting. The researchers concluded that given the choice between surgery, watchful waiting or external beam radiotherapy, patients younger than 50 with moderately or poorly differentiated prostate cancers have better long-term overall and cancer-specific survival when they select surgery. (Source: Press Release: Henry Ford Hospital, May 5, 2009)

Prostate Cancer Vaccine Improves Survival. The results of the so-called IMPACT study involved 512 men with minimally or asymptomatic, metastatic, castrate-resistant prostate cancers that were randomized in a 2:1 fashion to sipuleucel-T (Dendreon Corporation's *Provenge*) or a placebo. Prostate cancer immunotherapy with *Provenge* extended median survival by 4.1 months and improved 4-year survival by 38%. The vaccine was manufactured from the patient's leukocytes, which were expanded over a 2- or 3-day period and then reinfused on day 3 or 4 on an outpatient basis. Three cycles were given over the course of a month. *Provenge* extended median survival by 4.1 months; median survival was 25.8 months with active treatment and 21.7 months with placebo. An observer commented that this 4-month extension in survival is very significant. The patients had a life expectancy of about 2 years, so giving them 4 more months is important. It gives them about 20% more life and does it with minimal adverse events. Discomforts such as headache, chills, and flu-like symptoms were treatable with aspirin. Another observer said that the IMPACT study results may overcome earlier reservations about *Provenge* by the Food and Drug Administration. (Source: American Urological Association, 104th Annual Scientific Meeting: Abstract 9: presented April 28, 2009, via *Medscape Urology*)

Bone Health Management After Androgen-Deprivation Therapy. A study by Alibhai, et al., University Health Network, Toronto, revealed that few men with prostate cancer undergoing androgen-deprivation therapy (ADT) are told about its effects on bone density, and prevention efforts are not usual. Clinicians need to do a better job in advising such patients and in screening for osteoporosis. The researchers assessed bone health management practices using both clinician-reported documentation of patient encounters and patient interviews in 66 men starting ADT for non-metastatic prostate cancer. Before starting ADT, 28 of the men (42%) had normal bone mineral density (BMD), 35 (53%) had osteopenia, and 3 (5%) had osteoporosis; but the results of BMD tests were discussed with only 21% of patients by 3 months and 32% by 6 months.

Lifestyle changes to preserve bone health were discussed with only 11% of all patients, and pharmacological interventions were recommended to 18%, including 26% of men with osteopenia and 2 of 3 men with osteoporosis. Within 6 months of beginning ADT, 23% of men reported taking calcium and 38% reported taking vitamin D. Only 1 patient was taking a bisphosphonate at that point. Given the recent attention being paid to the bone side effects of ADT, the researchers had expected much better patient-physician communication regarding the side effects of ADT. They suggest ADT-bone health issue be improved by routinely providing appropriate written information about side effects of ADT to patients. Also, multidisciplinary clinics may help patients deal with the many side effects of ADT better than an individual clinician.

(Source*: BJU Int* 2009;103:753-757, via Reuters Health Information, April 16, 2009)

Prostate Cancer and Agent Orange. A new study confirms an earlier finding regarding Vietnam veterans exposed to Agent Orange. Vietnam veterans who undergo radical prostatectomy and who were exposed to Agent Orange are at increased risk for biochemical recurrence of prostate cancer. These veterans also had a shorter PSA doubling time than veterans who underwent the procedure, but who were not exposed to the toxic defoliant. Terris, et al., Charlie Norwood VA Medical Center, Augusta, GA, studied 1,495 veterans with prostate cancer who underwent radical prostatectomy, 206 of whom were exposed to Agent Orange. After the several adjustments for clinical factors, they found that the exposed patients had a 45% increased risk of their cancer biochemically recurring, as well as a shorter median PSA doubling time compared to the other veterans in the study.

The authors note that the clinical significance of the findings is not clear; nevertheless, the findings should be a red flag for clinicians who treat Vietnam veterans. The researchers recommend that clinicians be proactive with Vietnam veterans with prostate cancer and follow them closely for potential recurrence following treatment. However, one prostate cancer expert has noted that biochemical recurrence after definitive therapy is common and is often associated with an excellent prognosis. The researchers acknowledge other limitations in the study: e.g., the ability to quantify the levels of dioxin or Agent Orange is not yet available; and the participating veterans potentially had financial incentives to associate their diagnosis with a history of Agent Orange exposure. (Source: *BJU Int*. 2009:103;1168-1172 via Medscape Medical News, April 22, 2009)

AUA Guidance on PSA Screening. The American Urological Association (AUA) recently issued new clinical guidance which directly contrasts with recent recommendations issued by other major groups about prostate cancer screening. The use of the PSA test for prostate cancer screening is highly controversial; however, the AUA believes that, when offered and interpreted appropriately, the PSA test may provide essential information for the diagnosis, pre-treatment staging or risk assessment, and post-treatment monitoring of prostate cancer.

This new Best Practice Statement updates the AUA's previous guidance issued in 2000. Major changes include new recommendations about who should be considered for PSA testing, as well as when a biopsy is indicated following an abnormal PSA reading. According to the AUA, early detection and risk assessment of prostate cancer should be offered to well-informed men 40 years of age or older who have a life expectancy of at least 10 years. The future risk of prostate cancer is closely related to a man's PSA score; and a baseline PSA level above the median for age 40 is a strong predictor of prostate cancer. Such testing may not only allow for earlier detection of more curable cancers, but may also allow for more efficient, less frequent testing. Men who wish to be screened for prostate cancer should have both a PSA test and a digital rectal exam (DRE). The AUA statement also notes that other factors such as family history, age, overall health and ethnicity should be combined with the results of PSA testing and physical examination in order to better determine the risk of prostate cancer. The statement recommends that the benefits and risks of screening of prostate cancer be discussed with the patient, including the risk of over-detection, such as detecting some cancers which may not need immediate treatment.

An AUA spokesman said that "The single most important message of this statement is that prostate cancer testing is an individual decision that patients of any age should make in conjunction with their physicians and urologists. There is no single standard that applies to all men, nor should there be at this time." He also noted that the AUA panel carefully reviewed the most recently reported trials of PSA testing in both the United States and Europe before finalizing their guidelines.

In regard to biopsy, a continuum of risk exists at all PSA values, and major studies have demonstrated that there is no safe PSA value below which a man may be reassured that he does not have biopsy-detectable prostate cancer. Therefore, the AUA does not recommend a single PSA threshold at which a biopsy should be obtained. Rather, the decision to biopsy should take into account additional factors, including

free and total PSA, PSA velocity and density, patient age, family history, race/ethnicity, previous biopsy history and co-morbidities.

Additionally, the AUA statement emphasizes that not all prostate cancers require active treatment and that not all prostate cancers are life-threatening. The decision to proceed to active treatments is one that men should discuss in detail with their urologists to determine whether active treatment is necessary, or whether surveillance may be an option for their prostate cancer. (Source: AUA Press Release, April 27, 2009)

Learning Curves: Open Prostatectomy Versus Laparoscopic Procedures. According to a recent study, the risk for disease recurrence after a radical prostatectomy is strongly affected by the experience of the operating surgeon. This is true for both open and laparoscopic procedures. However, researchers report that the learning curve for surgery — i.e., improvement in surgical outcomes with increasing surgeon experience — appears to accrue more slowly for laparoscopic radical prostatectomy than for open surgery.

In an earlier study, Vickers, et al., Memorial Sloan-Kettering Cancer Center, New York, found that prostate cancer patients treated by highly experienced surgeons were far more likely to be cancer-free 5 years after surgery than patients treated by surgeons with less experience. In this recent study, the researchers conducted a retrospective multicenter cohort study of 4,702 patients with prostate cancer treated laparoscopically. They found that the probability of cancer recurrence after laparoscopic radical prostatectomy declined as the experience of the operating surgeon increased, but the surgical outcomes seemed to improve more slowly for laparoscopic than for open surgery. Their analysis showed that surgeons had to perform approximately 750 laparoscopic surgeries before they achieved the same low level of disease recurrence as other surgeons achieved after 250 traditional operations.

According to the authors, there are a number of possible explanations for this observation. One is that laparoscopic radical prostatectomy may be inherently more difficult to learn. Another reason is that in addition to increasing experience of an individual surgeon, the laparoscopic learning curve may reflect profession-wide modifications to the technique. Open radical prostatectomy is a relatively mature procedure, whereas laparoscopy is a much more recently developed surgical technique. If the data are replicable, these findings may have important implications for surgical practice because they suggest that surgeons should not switch back and forth between techniques without a compelling reason to do so. (Source: *Lancet Oncology* published online April 1, 2009, via Medscape Medical News, April 2, 2009)

Selenium Won't Go Away! The Center for Science in the Public Interest, a nonprofit consumer group, has filed a complaint with the Federal Trade Commission contending that Bayer HealthCare employs "deceptive and irresponsible" advertising regarding selenium in two of its multivitamin products. A law suit is also likely. Bayer's ads for One-A-Day Men's 50+ Advantage and One-A-Day Men's Health Formula multivitamins say selenium may cut men's risk of prostate cancer. Both dietary supplements contain 105 micrograms of the trace mineral selenium per daily dose, or about twice the Recommended Daily Allowance, which is 55 micrograms a day for adults, according to the center.

The Center for Science in the Public Interest's complaint is supported by other groups including the American Cancer Society. In its complaint the Center cited the Selenium and Vitamin E Cancer Prevention Trial (SELECT) involving 35,000 men that was halted when researchers determined that selenium was not protecting the men from prostate cancer and may have been causing diabetes in some of them.

A spokesperson for Bayer said the company was standing behind the claims made in support of the products. (Source: CNN – June 18, 2009)

VA Gets Black Eye! Ninety-two veterans were given incorrect radiation doses in a brachytherapy procedure during a six-year period at the Veterans Affairs Medical Center in Philadelphia. A hospital team that performed the procedure botched it on 92 of 116 occasions and continued the treatment for a year even though monitoring equipment was broken. Most of the veterans got significantly less than the prescribed dose

while others received excessive radiation to nearby tissue and organs. The medical center suspended its prostate cancer treatment program as a result of the ongoing investigation. The VA also suspended brachytherapy procedures at its hospitals in Jackson, MS, and Cincinnati. The problems at these locations were not as severe as those in Philadelphia.

All of the affected veterans subsequently received follow-up care, and eight got additional seed implants at other VA facilities. Four of the men have since died, but none of the deaths was connected to prostate cancer or the treatment. Regulators report there was evidence of problems as early as 2003, and cited the hospital leadership for failure to oversee the brachytherapy unit. The brachytherapy unit was staffed under contract to the University of Pennsylvania School of Medicine, and one doctor was responsible for most of the errors. He reportedly had limited experience with the brachytherapy procedure. The investigation continues. (Source: Associated Press-Monday, June 22, 2009)

Is Androgen-Deprivation Therapy Overused?

Two experts have challenged what they term the overuse of androgen-deprivation therapy (ADT) for prostate cancer in recent editorials in two prominent journals. Both Dr. Peter Albertsen, University of Connecticut, and Dr. William Dale, University of Chicago, agree that ADT has been shown to improve survival in men with metastatic prostate cancer, but that its survival benefits are mostly uncertain or unproven in other stages of the disease.

In the opinions of Dr. Albertsen and Dr. Dale, the overuse of ADT is attributable to several factors. It has been driven, in part, by clinicians in the United States overestimating the effectiveness of ADT on the basis that if it's effective for advanced disease, there's a good chance it will work for localized disease. There is also a propensity to “do something” about the cancer, particularly in older men, that leads to reliance on a therapy that is not justified. Two examples are early initiation of ADT when PSA first rises following surgery or radiation, and use in older men as primary therapy rather than surgery or radiation therapy. Dr. Albertsen also suggests a crasser motive, citing the profitability of the therapy, although he sees it as less of a motive of late.

In their editorials and comments, Drs. Albertsen and Dale encouraged clinicians to limit their use of ADT to appropriate patients. They reminded clinicians of the potential deleterious effects of treatment, including osteoporosis, fatigue, weakness, adiposity, worse cholesterol profiles, hot flashes, and now the development of diabetes. Dr. Albertsen advocates limiting ADT primarily to men with advanced localized disease undergoing radiation therapy and to men with clear signs of systemic disease, saying these patients are most likely to benefit from either symptom relief or increased survival that would justify the quality of life issues associated with ADT. Dr. Albertsen’s conclusion is based on the current literature, especially the recent European study of men with advanced localized disease published in the *New England Journal of Medicine*. The study indicates that, following external-beam radiation for locally advanced prostate cancer, 6 months of ADT does not provide survival superior to 3 years of treatment. In short, the study says that 3 years of ADT, which is the standard in this setting, should remain the standard. He stresses that the results should not be generalized to men with other stages of prostate cancer, citing differences in screening practices in the United States and Europe.

According to Dr. Dale, the best candidates for early use of ADT, in addition to patients with overt metastasis, are younger patients (under 65) with "high-risk" disease (e.g., high-grade prostate cancer, local spread of disease into lymph nodes) who are receiving external-beam radiation. Dr. Dale also suggested that otherwise healthy men with very high-risk features (Gleason grade of 8–10, PSA doubling times of less than 3 months, short time between primary therapy and rising PSA) could be started early. He emphasized that older patients with moderate-grade or lower disease and long PSA doubling times should not be started on ADT immediately. Dr. Dale also mentioned the need to balance the risk of the prostate cancer with the risks of the therapy because mixed information exists about the role ADT plays in worsening cardiovascular disease or diabetes. He notes that a recent study convincingly supports the conclusion that ADT contributes to the development of diabetes II. (Source: *J Clin Oncol*. 2009; published online

June 8, 2009; and *N Engl J Med*. 2009;360:2516-2525 and 2572-2574, via Medscape Medical News, June 11, 2009)

(Center for Prostate Disease Research—An Overview: Continued from page 1)

Clinical Research Program. Our Clinical Research Program has several elements. One is a multi-disciplinary, team approach to counsel newly diagnosed men about their conditions and their options for therapy. The patient meets with a urologic surgeon, a medical oncologist, a radiologist, and a patient educator to gain the insights he needs to make an informed treatment decision. Thus far over 1,500 patients have been seen in this manner and it has been a very successful program. In a related clinical program, we have teamed with medical oncologists from the National Cancer Institute for treatment of men with advanced prostate cancer after a failed primary therapy or who have become hormone refractory.

In recent years post-therapy quality of life has become a growing concern for patients. Knowing that our treatments cause side effects, we have developed a quality of life database that now contains over 1,300 patients. This permits us to better quantify those side effects while providing insights into how patients make treatment decisions and the sources of information they use to make those decisions.

We have more than 20 clinical trials underway and all of them are integrated with our basic science and multi-center databases. They cover the entire spectrum of prostate disease, including benign prostatic hyperplasia; prostate cancer prevention; early identification of high risk disease prostate cancer; comparisons regarding the efficacies of the primary therapies at various stages; rising PSA after primary therapy; metastatic disease; and hormone-refractory disease.

Benign Prostatic Hyperplasia. Now let's look at some of these clinical research efforts in more detail. First, let me say that the CPDR is not solely involved with prostate cancer, but rather, prostate disease. The lion's share of our efforts involves prostate cancer, but benign prostatic hyperplasia (BPH) cannot be neglected. You may be surprised by BPH prevalence by age group: 17% of men between 50-59 years of age; 27% of men between 60-69; and 35% of men between 70-79. Our BPH clinical trial is one of our longest efforts. Its title is Medical Therapy of Prostate Symptoms (MTOPS). The MTOPS study looked at what drug regimens are the best to maximize patients' quality of life by relieving their voiding symptoms. We essentially looked at two drugs-- finasteride and the alpha blocker doxazosin--and how they impact urinary function. The results were impressive. Those patients who received a placebo (no drug) had a much greater instance of progression of their symptoms as well as progression to urinary retention, and the need for a surgical procedure compared to patients who received a single drug. Participants who received a combination of finasteride and doxazosin had the best outcomes. In summary, the MTOPS study showed that combination therapy decreased by three times the progression of symptoms, lowered the risk of urinary retention, and the risk of needing a procedure to treat urinary symptoms. These important findings were published in the New England Journal of Medicine.

SELECT Prostate Cancer Prevention Trial. The CPDR was significantly involved in the SELECT Prostate Cancer Prevention Trial (PCPT). No doubt many of you are familiar with this important cancer prevention trial involving 36,000 men to determine whether selenium and vitamin E would decrease the risk of prostate cancer. An interim analysis performed after seven years revealed that there was no decrease in prostate cancer associated with selenium and vitamin E. In fact, there might have been a slight increase in patients in the vitamin E arm of the trial. There also were other health considerations that led to the SELECT Trial being halted as a prostate cancer prevention trial. Several sub-studies will continue for two more years to see whether selenium and vitamin D prevent cataracts and age-related macular degeneration, as well as the prevention of Alzheimer's disease. Hopefully, these sub-studies will provide some benefit.

Prostate Cancer Prevention Trial (PCPT). The next study I would like to talk about is the Prostate Cancer Prevention Trial (PCPT) which is likely to have considerable influence on clinical practice over the next several years. Essentially, it looked at patients who were placed on a placebo or finasteride (Proscar) and followed for seven years, at which time they were biopsied. Some patients were biopsied during the study for cause, i.e., they had an elevated PSA or an abnormal rectal exam during the course of the study. The study found that those participants on the placebo had a 24% chance of being diagnosed with prostate cancer, and those participants on Proscar had an 18% chance of being diagnosed with prostate cancer. This 25% relative risk reduction is significant and has changed the management of benign prostatic hyperplasia (BHP). Patients diagnosed with BPH are now being started on Proscar, not only as a treatment for their BPH symptoms, but also as a potential preventative mechanism for prostate cancer. Another finding from the study was unexpected. The participants biopsied at the end of the study were those with normal digital rectal exams and normal PSAs. Yet, fifteen percent of those participants actually developed prostate cancer, and of those so diagnosed, up to a quarter of them had high grade prostate cancer. This indicates that existing screening mechanisms may be inadequate.

Genprobe. The CPDR is cooperating with industry in a study called Genprobe. It seeks to develop urine tests in order to provide more specificity and prognostic value than PSA testing. We are looking at four molecular markers. Basically, the patients receive a prostatic massage, and then provide a urine sample for analysis. We are finding that these markers not only improve specificity over PSA alone, but also predict adverse pathologic features such as total tumor volume and the incidence of extracapsular extension (disease beyond the prostate). This is a very promising study that is still ongoing.

Quality of Life Considerations and Decision Making. We know that the various treatments for prostate cancer have inherently different quality of life outcomes. There is wide agreement that quality of life is an important end point in cancer research, even equal to such traditional measures as PSA recurrence and survival end points. In fact, many experts now hold that cancer trials are incomplete without a health-related quality of life assessment.

At the CPDR we are looking at how our treatments affect patients' quality of life so we can better counsel them regarding treatment decisions and outcomes. We have more than 1,000 men enrolled in our database. We use validated quality of life surveys to establish baselines prior to treatment, then we follow up at set time periods for up to three years. These surveys include such topical areas as hormonal, physical, urinary, sexual, and bowel functions. We have done many analyses on this database and we have presented several papers at professional conferences.

Let me give you an example. We found at baseline before treatment that African Americans have a worst baseline quality of life in urinary function, bowel bother, and hormonal bother when compared to Caucasians. We also know that Caucasians choose expectant management (watchful waiting) twice as frequently as African Americans; and Caucasians are three times more likely to choose surgery over radiation. We also found that African Americans disproportionately chose radiation alone over all other treatments as compared to Caucasians. But when we look at treatment outcomes, African Americans who underwent radiation therapy only differ from Caucasians in one domain, that is urinary function, and African Americans who underwent surgery only differ from Caucasians in one domain and that is physical function. So despite having significant health differences at the outset, the groups were about equal in outcomes after treatment. From this we can conclude that baseline health-related quality of life does differ between African Americans and Caucasians despite their being in our multidisciplinary, equal access healthcare system.

The concern is that these differences at baseline may lead to treatment selection bias and, in my opinion, unduly so. Therefore, we need to start counseling patients with regard to their health-related quality of life outcomes and not necessarily their baseline status. Furthermore, we should pay close attention to the reasons why African American men select external beam radiation therapy, and how this impacts their long

term urinary function. In short, these types of studies should raise the consciousness of providers and patients alike regarding the impact of therapy selection on health-related quality of life issues.

CALGB Punch Study. In the early-stage, localized prostate cancer spectrum, we have the CALGB Punch Study for patients with high risk prostate cancer that may not be cured by surgery alone. In this study we divided the patients into two arms; one is hormonal therapy plus chemotherapy (docetaxel) followed by prostatectomy and lymph node dissection. These patients are being compared to patients undergoing prostatectomy and lymph node dissection only. We already know that docetaxel is proven to prolong survival in patients with metastatic and large volume disease. The idea of our CALGB study is to achieve a similar effect at an earlier stage of disease where the burden is less.

In a related effort involving radiation, we are looking at a combination of hormones, taxotere and radiation in one group versus hormones and radiation only in the other group. Again, this study is aimed at early stage, aggressive prostate cancer in patients who may need combined therapy beyond surgery or radiation alone. Both studies hold promise for the future.

Viagra Study. This study seeks to enhance penile rehabilitation for patients who underwent a nerve-sparing prostatectomy. The hope is to rehabilitate the penis to restore those microvascular channels affecting erectile function. Then perhaps we can prevent some of the fibrosis and scarring that happens post-treatment, thereby improving erectile function as well as the speed with which it is restored. Here is how it works. Prior to surgery, we obtain a Ridgascan, a procedure that tests the actual function, strength, and frequency of the patient's erections. We also employ a questionnaire which quantifies the patient's erectile function. The participants are divided into two groups. One group receives a low dose of Viagra each night, and the second group receives a placebo. Participants in both groups also receive on-demand doses of Viagra as needed. We then measure the outcomes between the two groups. The study is still in progress.

Theralogix. This study examines the effect of a nutritional supplement on men with recurrent prostate cancer who have a PSA doubling time between three and twelve months. It is an oral pill that has minimal side effects, so patients tolerate it very well. We hope it will change the PSA dynamics. It is suitable for men who had any primary therapy, but participants must not be on hormonal therapy. The study is still in progress.

Sanofi/Encorium Study. This study focuses on patients with more aggressive recurrence than the Theralogix study does. It is specifically for patients with a rising PSA following prostatectomy and at high risk of progression. The men in one group are treated with hormones, docetaxel, and Casodex. The men in the second group get combination androgen blockade with leuprolide and Casodex. By adding docetaxel to the first patient group we hope the early institution of this chemotherapy will prevent further progression of PSA.

High Intensity Focused Ultrasound (HIFU). This is a treatment for patients with recurrent disease after radiation therapies that are looking at a second chance for a local cure. Many of you know that salvage radiation is an option for PSA recurrence after surgery. But if you have failed radiation, you don't have a good salvage regimen. That is why we are interested in this technology. It works like this. We place a probe in the rectum much like a prostate biopsy probe. We visualize the prostate on ultrasound and then focus high intensity ultrasound waves on the prostate to promote tissue destruction. HIFU has several advantages. It is minimally invasive, it avoids reliance on hormonal therapy, and the only other interventions needed are a suprapubic drainage tube and a Foley catheter post-therapy. We employ temperature probes and power adjustments to tailor therapy for specific regions. This therapy is very exciting and very promising. We have treated two patients with it thus far at Walter Reed and the trial is ongoing.

TARP Study. In my earlier remarks we were dealing with BPH, disease prevention, local disease, and then recurrence without evidence of metastatic disease. Now, we move along our prostate cancer continuum to studies affecting

patients with metastatic disease. The Therapy Assessed by Rising PSA (TARP) Study evaluates the effectiveness of providing additional hormonal therapy to patients who have failed first-line androgen deprivation. We combine Casodex and dutasteride for 18 months and compare the outcomes to patients receiving Casodex only. Our primary end point is the time to PSA progression or metastatic disease.

Dendreon. The CPDR has been involved for some time in the Dendreon study. If you follow the news, you are likely aware of the recent announcement showing that Dendreon's *Provenge* is the only vaccine therapy to demonstrate survival effectiveness in patients with metastatic disease. The study involved patients with androgen-independent metastatic prostate cancer and found that *Provenge* could extend median survival by four months. It also increased three-year survival by 38% compared to a placebo. This is the first demonstration of active cellular immunotherapy to prolong survival. Although three or four months may seem brief, the Dendreon study sets the stage for future research in this area because now we know that immunotherapy has the potential to work even in the setting of advanced metastatic disease.

That has led us to a follow-on trial called BNIT, again a prostate cancer vaccine. This is a phase one trial essentially looking at dosing, absorption and drug efficacy for patients who have a rising PSA after hormonal therapy, but who don't have metastatic disease. The idea is to treat patients earlier knowing that the earlier we can institute treatment, the higher chance of success.

AstraZeneca Trials. Finally, I would like to talk about our AstraZeneca trials. This very day AstraZeneca issued an announcement regarding its new drug ZD4054, said to prolong survival in men with metastatic disease by between 3 to 4 months. This is hot off the press. We have three studies ongoing with this drug. It is an endothelial cell antagonist. It is supposed to decrease the amount of new vasculature and new blood flow to tumors, as well as decrease the cell interaction to promote cancer-cell death. The three trials here at the CPDR involve men with hormone-refractory prostate cancer with (1) no metastatic disease; (2) bone and soft tissue metastatic disease without pain; and then (3) with pain.

This has been a quick overview of current research here at the CPDR. I trust you find it encouraging to know the extent of the research, both basic and clinical, that is underway. We are always seeking volunteer participants in our trials, so if you or someone you know are eligible and interested, talk to me after the meeting and we can pursue the matter.

USING YOUR DATA AND YOUR PROSTATE!

Have you ever wondered what we do with the information after we solicit your involvement in our database and the use of your prostate for research? Let me give you an example by describing a research study we recently presented at the American Urological Association's annual conference. It deals with single-focus (or unifocal) therapy for prostate cancer, i.e., treating just one portion of the prostate, leaving the remainder intact.

The interest in single-focus therapy is part of the increasing emphasis on limiting the quality of life impact of prostate cancer therapy. There are some difficulties. We must rely on prostate mapping to confirm the presence of unifocal or single-focus disease. And prostate mapping has some problems with it. Furthermore, there has been slight research into the tumor biology of single-focal disease and how it may differ from multi-focal disease. You may intuitively think that single-focal disease is less aggressive, but it may be more aggressive. Or it may be a coalescence of multiple cancers into one and be later-stage disease. So more investigation into single-focal prostate cancer is essential, but we have to start somewhere.

Here is what we did. We looked at our (your) prostate specimens obtained from our tumor database for a ten-year period and quantified the number of tumor foci and correlated these pathologic specimens with our clinical and pathologic data. We divided our sample into two cohorts – that is, men with either unifocal disease or multifocal disease. The median ages between each cohort were the same. We found that out of more than 1,000 prostates about ten percent had single-focal disease. The overall

outcomes were seemingly counter-intuitive: (a) the PSA in patients with unifocal disease was significantly higher than those with multifocal disease; (b) their tumor volume, although it was only one focus, was higher than the aggregate tumor volume of patients with multi-focal disease; (c) on prostatectomy, their incidence of disease outside of the prostate was much higher than those with multifocal disease; (d) the patients with unifocal prostate cancer had a much higher incidence of high-grade cancer; (e) regarding biochemical recurrence, we found that patients with unifocal disease had a much higher and statistically significant incidence of biochemical recurrence, even for patients with organ-confined disease.

Our hope is to continue this research effort, perhaps using molecular mechanisms to predict aggressiveness, and possibly by coupling it with our other studies such as Genprobe mentioned earlier. The development of predictive models would help us select the patients most appropriate for treatment in this manner.

Asian-Americans and Prostate Cancer

Finally, I want to mention one other demographic and epidemiologic study we have ongoing regarding Asian-Americans and prostate cancer. We became interested because we noted a marked increase in the incidence of prostate cancer among Asian-Americans. We also know that Asian-Americans have a higher annual death rate from cancer exceeding their death rate from cardiovascular disease, which is different from the remainder of the US population. Asians residing in North America often present with more advanced clinical stages and higher tumor grades than Caucasians, and in some studies, even African Americans.

This moved us to examine our database to determine what was the case within an equal-access medical center. We had to include some cultural factors. Sociologic studies show that Asian-Americans have a pervasive view that a cancer diagnosis is synonymous with a death sentence. Cancer is not a subject that they discuss publicly, so they are less apt to seek care for the disease. There also may be language barriers and access-to-care issues existent in that cultural subset.

Upon examining our database, we found 600 Asian-Americans out of 11,000 patients that met our inclusion criteria. We compared them with other racial subgroups and found that Asian-Americans were younger at diagnosis, had lower clinical stages, but higher biopsy grades than Caucasians and African Americans. The Asian-Americans were also more likely to choose prostatectomy as a primary mode of treatment with a propensity towards robotic or laparoscopic techniques. After pathologic analysis, we found that Asian-Americans had significantly lower pathological stages, i.e., better tumor prognosis and a trend towards lower pathologic Gleason grade. The incidence of positive margins among all our racial subgroups was the same. But when we looked at these patients over the long term, we found that Asian-Americans had a significantly lower overall mortality from their prostate cancer--five percent compared with Caucasians (22.5%) or African Americans (21.6%). So Asian-Americans are doing much better in our system.

This could be due to several factors such as differences in BMI. We also know that there are certain genetic polymorphisms present in Asian-Americans that affect how their androgen receptors responds. Androgen receptors are essentially a linkage between testosterone and tumor. So they may be responding to testosterone differently than other racial subgroups because of these genetic polymorphisms. We also know that certain hormone levels such as 5 alpha reductase are much lower in Asian-Americans. So all these factors may be affecting outcomes.

Summary. In summary, I want to emphasize that CPDR is very active in multiple realms of research from clinical studies to new treatment modalities to demographic and epidemiologic studies and genetic investigations. We have a varied and comprehensive research platform where we integrate our clinical database and basic science research. In the process, we work to improve our quality of care, including patient counseling, by offering new therapies so we can be on the cutting edge of prostate cancer management, and by identifying the best sequence of treatments to obtain the best outcomes.

Thank you very much for your time and interest. If you have any questions, I would be more than happy to answer them.

Question: Within the data you displayed regarding Asian-Americans, the actual number of cases was very low. Wouldn't this affect the statistical significance of the outcomes?

Answer: The numbers that you saw on the last slide were the number of deaths, not number of patients treated. That is why they appear to be very low. For some reason, yet to be determined, it seems that Asian-Americans are responding much better to prostate cancer treatment compared to other racial subgroups within the database

Question: What is the medical community's general attitude with regard to prostate cancer survivors taking multivitamins?

Answer: Speaking for myself, I don't see multivitamins providing any distinctive benefit. This topic deserves more research regarding which multivitamins and dosages may be beneficial. Several studies in the general medical literature found that multivitamins don't improve survival or quality of life, and certainly from the studies we have done thus far, we have not seen any impact of multivitamin therapy on prostate cancer outcomes.

Question: In the early part of your presentation, you mentioned preventive measures that might be useful for men with BPH.

Answer: In the realm of preventive measures, the Prostate Cancer Prevention Trial (PCPT) has had the most impact. If a patient were to come to me with significant voiding symptoms, an enlarged prostate, and a slightly elevated PSA, I would be inclined to start him on Proscar, not only to deal with his voiding symptoms, but also because the PCPT suggests that it may decrease his risk of prostate cancer. There is an added benefit because Proscar shrinks the prostate gland, thereby enhancing the diagnostic accuracy of any subsequent prostate biopsy. I am enthusiastic about Proscar for these reasons.

Question: Suppose I have a series of ultrasensitive measurements and you notice a steady increase in doubling time, at what point would intervention be appropriate?

Answer: Let's say that after prostatectomy, you noticed a linear increase of your PSA, but you had not reached the "magic" value of 0.2 ng/ml which is widely held as evidence of cancer recurrence. Some patients in that situation seek, and some providers would counsel, radiation therapy as a salvage regimen prior to your PSA actually getting to the 0.2 level. I think that is the trend among most providers.

There was a recent study by a major radiation therapy group that looked at patients who after prostatectomy had worrisome pathology, i.e., high Gleason scores after pathology, extracapsular extension, positive margins, or seminal vesicle involvement. Yet all these patients had undetectable PSAs post-operatively. They were divided into two groups. One group was immediately treated with radiation despite having an undetectable PSA. The other group was followed until the patients reached a PSA of 0.2 or higher, and then were treated with radiation. The researchers found that the patients who were treated immediately did much better than those who were treated after they had clinical recurrence. In a situation where you had ultrasensitive PSA rising in a linear fashion after prostatectomy, I would likely be inclined to recommend radiation therapy at that point.

Question: One year after surgery, I had the very slight rise in PSA, and a Prostascint was ordered. Would you care to comment?

Answer: The value of the Prostascint has been widely discounted for multiple reasons. The procedure is expensive and time-consuming. Furthermore, many hospitals do not have the volume necessary for the radiologist to develop and maintain the skill sets required for interpretation. Here at Walter Reed we have a high volume operation and an experienced staff, so in clinical situations such as we enjoy here, I am very comfortable ordering the Prostascint and relying on it for treatment decisions.

Question: What is the status of imaging technology today, especially as it might reduce the need for biopsy?

Answer: That's a great question! Thus far imaging technology has not supplanted biopsy for confirming the presence of cancer. We actually need tissue. Where we see advances in imaging technology is in the more accurate placement of the biopsy needle. Let me give you an example. A patient undergoes four prostate biopsies; his prostate volume is 40 grams, his PSA is 15 ng/ml and rising, and his percent free PSA is very low. As a doctor, I know he's got prostate cancer, yet the four biopsies cannot confirm it.

Some imaging technologies, such as the PET scan and MRI spectroscopy, provide specific imaging modalities allowing us to identify tumor location. We then can overlay those images with our ultrasound and direct the needle into that location. At the National Cancer Institute they are actually doing MRI- guided biopsies. It is labor intensive and expensive, so only specialized centers can afford it. In short, imaging technology is very helpful in obtaining tissue, but it does not provide tissue diagnosis.

Question: Nutrition continues to be touted as the key to cancer prevention. I have always had what I thought to be good nutritional habits, and I have participated regularly in 10K races and marathons, but that apparently didn't help me—I will soon have a radical prostatectomy! Can you comment on the preventive value of nutrition pre-surgery and post-surgery?

Answer: Many patients are interested in just that topic. What can I do in the nutritional sense to prevent cancer, or to deal with cancer after therapy? Many of these studies are questionable in design and statistical method. No one should be relying solely on a specific diet or supplement to work for them. Think about it this way. Your chances of dying of cardiovascular disease are probably much greater than dying of prostate cancer. So anything you can do to maximize your overall cardiac health will benefit you much more than anything you can do to affect your prostate cancer. Yes, it is true that high fat diets place oxidative stress on the body likely leading to more advanced, aggressive cancers or a higher incidence of the disease. On the other hand, the value of eating right (a balanced, high fiber, low fat diet) and exercising regularly offer the greatest benefit in the cardiovascular realm than in the cancer realm.

Comment from the audience: WRAMC offers a cardiovascular health program through its Integrated Cardiac Health Program (ICHIP). After establishing a baseline health profile, the participants receive information on healthy diet, exercise, and stress management, set personal goals, and are evaluated periodically to measure improvement. This is a voluntary, self-referral program that is highly praised by the participants. More information is available at the CPDR.

Question: I had external beam radiation in 2006 and since then my quarterly PSAs have been up and down like a yoyo. Would the ultrasensitive PSA be helpful here?

Answer: In that situation the ultrasensitive PSA probably does not offer much utility. What you cite is a common complaint from persons who chose radiation therapy. The varying readings over time can be frustrating to the patient. The so-called "PSA bounce" is a well-described phenomenon after radiation, but the ultrasensitive PSA will not add any more information. The "PSA bounce" usually ends three years post-therapy; then it will be possible to obtain a reliable baseline PSA level.

Question: Is there any relationship between brachytherapy and increased risk for colon cancer?

Answer: There is some increased risk of colon cancer from brachytherapy and external beam radiation therapy—something on the order of 2 to 3 percent. And over the long term, there are also some bladder and rectal concerns from radiation therapy.

Question: Getting back again to cancer prevention through nutrition, we have seen that selenium, lycopene, vitamin E, and the like, have no reliable scientific basis. But now we are hearing more about the potential for vitamin D to be cancer-preventative.

Answer: I don't want to pre-judge any on-going research before the studies are published, but I am not optimistic. As I mentioned earlier, when

it comes to cancer prevention, the most convincing, reproducible study is the Prostate Cancer Prevention Trial regarding finasteride or the five alpha reductas. Vitamin supplements and dietary changes may decrease one's relative risk slightly, but not significantly, and certainly not to the extent that a medicine like Proscar would.

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Clinical Psychologist, WRAMC
Consultant to the Center for Prostate Disease Research

♦ TOPIC ♦

"Why Talking is Important, or Why 'Sucking it Up' Doesn't Work!"