WRAMC US TOO, Inc.

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NEWSLETTER

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♦ Prostate Cancer Research Program Funds $10 Million Research Consortium ♦

by Gail Whitehead
Congressionally Directed Medical Research Program

Every year, an estimated 220,000 American men will be diagnosed with prostate cancer; 31,000 will die from the disease. Although more men are being diagnosed and treated earlier, there remain some disturbing statistics. Among men over 65 years of age, African American men are twice as likely to die from prostate cancer as Caucasian Americans; they are three times more likely than Caucasian Americans to die if they are diagnosed with the disease when they are younger than 65. Leaders in prostate cancer research point out that understanding why these differences occur could lead to lower mortality rates for all men.

In 1997, Congress provided the Department of Defense with a $45 million dollar appropriation to establish a Prostate Cancer Research Program, managed by the U.S. Army Medical Research and Materiel Command. During the formation of the program, national experts in prostate cancer identified underfunded areas of research. Numerous research problems were evident and began to be addressed by the Prostate Cancer Research Program (PCRP), among them was the issue of differences in mortality among racial groups. Early studies funded were conducted by small research teams at individual research centers looking at factors such as diet, access to health care, biology of tumors, demography, etc. However, no single factor seemed to explain the differences in mortality rates between racial groups.

"It was time for another approach. PCRP national scientists, prostate cancer survivors and Army managers met and considered the research needed. They asked, 'What if we put aside all the issues of how this research has been funded and conducted in the past and put the best prostate cancer researchers in the United States on the same team, regardless of institution or where they live, and through the synergy of those efforts let the team find new answers to the overarching research questions in prostate cancer?' We offered funding to develop prostate cancer consortiums to address these questions," said Leo Giambarresi, the Prostate Cancer Research Program's program manager. **(Continued on page 7)**

♦ *INSIDE THIS ISSUE* ♦

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♦ FROM THE EDITOR'S DESK ♦

Personal Accounts and "The Doctor Is In"

Personal accounts of dealing with prostate cancer are among the most popular features of the newsletter. If you had a unique or interesting experience in combating the disease, consider sharing it with our readers. Please contact me if you are interested. "The Doctor Is In" is another popular feature that Dr. Judd Moul provided for 12 years. We will strive to maintain this feature. Dr. James Jezior, Department of Urology, WRAMC, is our guest contributor in this issue.

Our speaker for the August meeting was Dr. Nancy A. Dawson, Director, Genito-Urinary Medical Oncology, Greenebaum Cancer Center, University of Maryland. Her topic was "Recurrent Prostate Cancer" which addressed the therapeutic options available to men whose prostate cancer returns. A summary of Dr. Dawson's wide-ranging, informative remarks is presented beginning on page 9.

♦ PROGRAM FOR NOVEMBER 3, 2004 ♦

No doubt you have been hearing about the breakthroughs in surgical technique such as laparoscopic and robotic surgery. But do you understand how they really work and how they compare with the more conventional therapies for prostate cancer? Now you have the opportunity to hear from an expert in the these techniques. Dr. Jason D. Engel, Clinical Director of Urologic Laparoscopy, Center for Robotic Surgery, The George Washington University Hospital, is our November speaker. Certified in laparoscopic, laser, and robotic surgery, Dr. Engel will introduce us to the da Vinci robotic surgical system with his presentation - **New Techniques: The da Vinci Robotic Surgical System**. **Join us at 7 PM on Wednesday, November 3, 2004, in Joel Auditorium at WRAMC**. Plan now to attend and bring your spouse or a friend. They are always welcome.

♦ **Concerned About Incontinence?** The National Association For Continence (NAFC), dedicated to educating persons with bladder control problems, has developed a bladder health assessment tool to help such persons understand the condition and appropriate management options and treatments. Visit the NAFC web site at www.nafc.org to access this tool on-line. (Source: *The Washington Post* Health Section, September 21, 2004)

♦ **Biopsy Gleason Score Only An Estimate Of Final Pathological Gleason Score.** The Gleason score based on core biopsies may differ significantly from the final Gleason score based on analysis of the entire prostate removed during radical prostatectomy. A recent study by researchers at the University of Miami School of Medicine underlines this fact. They evaluated 531 core biopsies that had been assigned a Gleason score of 3+3 = 6 followed by a full analysis of the removed prostates. Agreement was found in only 51% of the cases. The postoperative Gleason score was higher in 41% and lower in 8% of the specimens. In the upgraded specimens, extraprostatic tumor extension was found in 22% compared to 4% of those that remained at Gleason 6; similarly, seminal vesicle involvement was found in 9% compared to 2%. At a 55-month follow-up, the risk of biochemical recurrence was three times higher in patients whose specimens were upgraded after surgery. The study demonstrates the limitation of random core biopsies in determining the tumor heterogeneity and multifocality and the challenge it poses for physicians in counseling patients about treatment choices and outcomes based on core biopsy data. (Source: *Pca Commentary*, Vol. 24, page 4: September 2004)

♦ **Combining Modalities Increases Prostate Cancer Cure Rates.** Stock, et al., at Mount Sinai School of Medicine found that combining hormonal therapy, brachytherapy, and external beam radiation therapy (EBRT) for high-risk prostate cancer patients increased the chance of cancer cure. Previous studies showed the 5-year freedom from recurrence rates for high-risk patients treated by just one primary therapy to be between 0 and 50%. The researchers studied 132 men with high Gleason scores, high PSA scores or who had an advanced clinical stage of prostate cancer. A combination of hormonal therapy, brachytherapy and EBRT produced an 86% rate of freedom from recurrence after five years. Also, 47 of the original 132 patients had a prostate biopsy after two years and all of them showed no evidence of cancer recurrence. The researchers conclud- ed that the combined therapies can be very effective for men with aggressive disease, and that the data supports the theory that enhanced local control can improve overall disease control. (Source: *Intern'l J Rad, Onc, Biol, Phy*; August 1, 2004, via Mount Sinai News, August 12, 2004)

♦ **Surgery Versus Radiation for Prostate Cancer.** It is widely assumed that treatment results of radical prostatectomy and radiation therapy (external beam and brachytherapy) are similar in outcomes. Prostate cancer patients who fail their selected primary therapy, whether surgery or radiation, are usually treated by androgen ablation. Researchers at Cancer Care

Northwest, Spokane, WA, conducted a small-sample study of patients who had failed either surgery or radiation. They evaluated survival outcomes following androgen ablation for recurrent prostate cancer in 161 men. Surgery offered a better survival rate compared to radiation. At five years of follow-up after beginning androgen therapy, 78% of the 94 patients who had radiation as primary therapy had died, compared to 63% of those who had a radical prostatectomy. The biggest difference in survival appeared to be those with metastatic disease, where 93% of patients treated with radiation died at a median of 2.34 years, compared to 69% who died at a median of 3.27 years following surgery. The report of the study is in the August 2004 issue of the *Journal of Urology*. A commentator noted that the study needs be confirmed by other analyses. He also says the study outcome has two possible explanations. First, that radiated patients were immunosuppressed and unable to control micro-metastatic disease as well as unirradiated patients; or second, that the two groups of patients differed at time of diagnosis since this was not a randomized study and that the results are due to higher-risk patients being in the radiated group. (Source: *J of Urol* 2004;172:525-528 via Cancer Consultants.com; October 4, 2004)

♦ **Nutrition and Prostate Cancer.** A review of foods and supplements that may affect the development or spread of prostate cancer led the Center for Science in the Public Interest to present a feature article entitled *Prostate Cancer: More Questions than Answers*. The article reviewed the scientific literature and consulted experts regarding nutrition and prostate cancer. Flaxseed, calcium, fish versus meat, green tea, low-fat diet, selenium, soy, lycopene, vitamin E, and zinc–the foods and supplements most frequently touted in the popular media–were considered. Not surprisingly, the scientific jury is still out regarding their efficacy. The article also notes the potential concerns associated with reliance on some of these foods and supplements. The article offers this "bottom line:" (1) Cut back on red meat and shoot for two or three servings of fish a week; (2) Try for at least two servings a week of tomato sauce (preferably on pasta or other dishes not heavy in cheese; (3) Take a multivitamin with roughly a day's worth of vitamin E (30 IU) and selenium (55 mcg); (4) Don't take more zinc than you get in an ordinary multivitamin (15 mg); (5) Don't assume that more calcium is better, so don't exceed the recommended calcium intakes (1,200 mg a day for men over 50, and 1,000 mg a day for men 50 and under, from food and supplements combined); (6) Avoid flaxseed oil supplements until research provides more information about alpha-linolenic acid (ALA). (Source: *NUTRITION ACTION Health Letter*: Center for Science in the Public Interest: Vol 31; No 6; July/August 2004)

♦ **Anesthesia for Radical Retropubic Prostatectomy.** General anesthesia reportedly is the most frequently used form of anesthesia for the radical retropubic prostatectomy (RRP). Researchers at the University Vita-Salute San Raffaele, Milan, Italy, found that spinal anesthesia was better than general anesthesia in a prospective randomized trial.. In this study, 72 patients with clinically localized prostate cancer were randomized to receive general or spinal anesthesia. Mean operative time and postoperative pain on day one were not significantly different. Those receiving spinal anesthesia had less overall blood loss, shorter time in the postoperative holding area, better pain outcome in the postoperative holding area, lower postopera-

tive sedation score, more patients passing flatus on day one, and better overall gait. The researchers concluded that spinal anesthesia allows good muscle relaxation and successful surgical outcome in patients undergoing RRP with pelvic lymphadenectomy for localized prostate cancer. There is less interoperative blood loss, less postoperative pain and faster postoperative recovery than general anesthesia. (Source: *Urology*:.2004;64:95-100 via Medscape, July 28, 2004)

♦ **PSA Usefulness Still Being Questioned**. In yet another challenge to the value of the PSA as a marker for prostate cancer, researchers at Stanford University say it is now clear that benign growth of the prostate is the most common cause of a PSA level between 1 and 10 ng/ml. Dr. Thomas A. Stamey had earlier held that the PSA could be used as a marker for prostate cancer, but increasing evidence that the PSA is not very sensitive led Stamey, et al., to pursue the matter. They examined tissue from 1,317 radical prostatectomies performed at Stanford since 1983 to compare the findings with the patients' PSA levels and other preoperative characteristics. Comparing 1983-88 with 1999-2003, they found dramatic decreases in cancers detectable by digital rectal examination, average volume of the largest cancer, and mean capsular penetration. Mean PSA levels had declined from 24.74 to 8.14 ng/ml during the same time frames. During 1983-88, six histolic features were significantly associated with PSA, but by 1999-2003, the only trail related to PSA was prostate weight. Given that most men will develop the disease if they live long enough and given its low associated mortality rate, it appears that dependence on the PSA has led to overtreatment of men with prostate hyperplasia. The authors conclude that the current extensive use of the PSA is unwarranted. Until a better marker is available, they recommend better training in the careful palpitation of the prostate, especially with the patient in the "knee-chest" position on the examination table. The researchers do note that the PSA will remain useful as a marker for benign prostatic hypertrophy and its rate of progression, as well as a marker for failure to cure after radical prostatectomy and probably for radiotherapy as well. (Source: *J of Urology*: October, 2004 via Medscape and Reuters Health Info, August 26, 2004)

♦ **Life After Prostate Cancer Treatment.** Men who had treatment for localized prostate cancer may be affected by erectile dysfunction and incontinence, but overall, their general health does not differ significantly from other aging men. While treatment for localized prostate cancer appeared to speed the decline in sexual and urinary function normally associated with aging, the treatment had no effect on other indicators of health-related quality of life. In a recent study, researchers followed 210 men who were treated for prostate cancer and 423 men healthy men for five years. Most of the men were over 60 years old. The study showed that men who had a radical prostatectomy appeared to suffer the most significant decline in sexual and urinary function. Radiation appeared to affect sexual but not urinary function. Overall, the researchers found no significant difference in health-related quality-of-life scores between the prostate cancer-treated men and the otherwise healthy men after five years. (Source: *Cancer*, 2004, Vol 101 via WebMD, October 4, 2004)

Lieutenant Colonel James Jezior, MC, USA

(Editor's Note: Readers should not act on the responses without prior consultation with their own physicians.)

QUESTION. I had a radical prostatectomy in 1995. After persistent incontinence, I had an artificial urinary sphincter (AUS) implanted in 1998. I find it generally satisfactory, but I am concerned if it places limits on physical activity. Are bicycling and horseback riding reasonable activities for a person in my situation?

ANSWER. It is not advisable to engage in activities that might traumatize the artificial urinary sphincter (AUS) and urethra. I advise my patients with an AUS (and those who have had complex urethral reconstructions) to avoid repeated trauma to the perineum that is inherent in cycling, horseback riding, and motorcycle riding. For those who are committed to cycling, there are seats available made to reduce perineal impact using a center hole, soft gel padding, and wider frames. In general, while no specific studies validate these recommendations, the risk to these surgical procedures make it prudent to protect them by relatively minor alterations in life-style. If complete avoidance of these activities is not possible, reduced participation with adequate time for healing between episodes should be considered.

QUESTION. I am 82 years old. I had radiation for my prostate cancer in 2000. My PSA has remained at about 0.2 ng/ml throughout. Now four years later, I have difficulty urinating. After examination, my physician advises that the condition is caused by the growth of my prostate and not by the growth of my cancer. He prescribed Flomax and Detrol for now, but has suggested either a TURP or Cooled Microwave Thermo Therapy. Frankly, given my age, I dislike both alternatives, and would be happy to rely on the Flomax and Detrol, but I want to do what is best in the long run. Is the growth of the prostate after radiation an unusual situation? How tried, tested, effective, and safe is the Cooled Microwave Thermo Therapy?

ANSWER. Lower urinary tract symptoms (LUTS) can occur from many conditions, the most common being bladder obstruction from prostate enlargement. Men who have undergone radiation therapy, however, can have other causes. The bladder is sensitive to radiation and can undergo chronic changes that leave it irritable, more likely to contract when the patient is not prepared to void. This is called an “overactive bladder.” In addition, obstruction does not have to occur from prostate enlargement; it can occur from scarring of the prostatic urethra or bladder neck known as a stricture or contracture depending on the location. Finally, other medical conditions of aging can leave our bladders either unresponsive or overly responsive that we see as LUTS. Some common conditions are: diabetes, Parkinson’s disease, stroke, heart failure, leg swelling, and medicine interactions. It is important to properly diagnose the cause of these urinary symptoms in the post-radiation patient because surgical intervention by any

method (electrical current, microwave, or thermal energy) has higher risks of incontinence and stricture formation, and if their cause is not obstruction, even failure. It must be noted that prostate size is far more likely to shrink following radiation and therefore symptoms are more likely caused by radiation changes rather than benign prostatic hyperplasia (BPH). Understanding a patient's voiding situation prior to radiation can help shape the treatment options available to him.

(PCRP Consortium - Continued from page 1)

Dr. James L. Mohler of Roswell Park Cancer Institute proposed such a team looking at prostate cancer health disparities and competed and received a consortium award. He remains a member of the University of North Carolina at Chapel Hill Lineberger Comprehensive Cancer Center and adjunct associate professor of surgery and pathology at UNC's School of Medicine, where he led the prostate cancer research program for 16 years. His work placed him in the unique position of having conducted prostate cancer research in the state with the highest African American mortality rates due to prostate cancer.

Three reasons have been suggested for the disproportionate prostate cancer mortality between the races, Mohler said. "First, African Americans may present more often with advanced, incurable prostate cancer because of limited access to health care, or they may be less likely than Caucasian Americans to choose effective treatments for potentially curable prostate cancer. For example, African Americans have been reported more likely to observe their prostate cancer. Secondly, biological differences between the races may cause the prostate cancer to develop at a younger age or spread more rapidly in African Americans. And finally, prostate cancers that occur in African Americans may be inherently more aggressive," he said. A national team of experts looking at comparable data in a scientific manner may provide some guidance about how best to allocate health care resources to reduce prostate cancer deaths, Mohler added.

Mohler's consideration of these issues led to the proposal to combine the strengths of scientists from 13 institutions into a national Prostate Cancer Project and to his collaboration with Dr. Elizabeth Fontham, dean of the School of Public Health at the Louisiana State University Health Science Center and associate director of the Stanley Scott Cancer Center. Louisiana has one of the lowest mortality rates due to prostate cancer among African Americans.

Other scientists from Harvard, Johns Hopkins, Boston, Duke and Wake Forest universities, the universities of South Carolina and California at Irvine, as well as the Roswell Park Cancer Institute, the National Cancer Institute, the National Institute of Environmental Health Sciences and the U.S. Food and Drug Administration, agreed to join Mohler and Fontham in this consortium. Mohler's proposal was one of two consortium awards from the DoD Congressionally Directed Medical Research Program. The other award went to Emory University in Atlanta.

Working together, the Prostate Cancer Project team designed a project using two parallel studies. Two thousand newly diagnosed prostate cancer patients will be enrolled in the studies: 1,000 patients--including 500 African Americans--from Louisiana and 1,000 patients--

including 500 African Americans--from North Carolina will be identified and recruited to participate in the program. This phase of the Prostate Cancer Project began this month.

"The patients will have in-home diet and health care interviews and blood and tissue sampling within 90 days of diagnosis." Fontham said. "New techniques in analyzing these samples will provide information about underlying factors effecting tumor growth for use by the Prostate Cancer Project team."

Having comparative groups in the two states is important, Dr. Fontham noted. "Caucasian Americans have similar prostate cancer incidence and mortality rates in both states, and their rate is much lower than African Americans. Comparing these differences statistically among the groups provides another test of significance," she said. "For example, the diet in Louisiana has more seafood than the pork diet of North Carolina. The difference in diet between the two states may interact with race to contribute to the biological differences in the prostate cancers between the African and Caucasian American patients. If that were the case, we could find ways to predict those men at higher risk for prostate cancer, and their physicians could help them detect prostate cancer earlier when it can be more successfully treated."

As the consortium moves forward and begins to obtain results, the administrative efforts seem well worthwhile. "It wasn't easy, but the potential for research that may help lower the mortality rate of prostate cancer and remove the health disparity between racial groups is a very compelling goal. Keeping that goal in mind moved us all to be flexible and diligent to make the Prostate Cancer Project Consortium Award possible," said Col. Kenneth Bertram, director of the Congressionally Directed Medical Research Programs. "Research such as the Prostate Cancer Project will help us find new answers for better prevention, diagnosis, treatment and, finally, the elimination of this terrible disease." Bertram, a physician, stressed the need for men to be screened for prostate cancer. "The American Cancer Society recommends that at age 50 men should go to their doctor and be screened for prostate cancer. Men at high risk, such as African Americans and men who have a first-degree relative (father, brother or son) diagnosed with prostate cancer at an early age, younger than age 65, should begin testing at age 45," he said.

JOHN A. PAGE LEAVES US TOO INTERNATIONAL

After more than four years of dedicated service, John A. Page is stepping down as President and CEO of US TOO International. Lewis C. Musgrove, chairman of the board, said Page made a lasting impression on the organization and persons it serves. During his tenure Page strengthened the local chapter structure involving over 350 locations worldwide, developed a committed volunteer base, led and trained a capable staff, and fostered collaboration within the prostate cancer community. He leaves an organization that is stronger, more energized, and more influential than ever before. Mr. Page will remain in office until October 31. It is anticipated that the organization will appoint an interim CEO while the board of directors conducts a search for a permanent replacement.

Recurrent Prostate Cancer

Nancy A. Dawson, MD
Greenebaum Cancer Center
University of Maryland

(A summary of a presentation to the WRAMC US TOO on Augusat 4, 2004)

Introduction

I am pleased to be back at WRAMC tonight. I'm going to talk about recurrent prostate cancer, covering the whole spectrum. I will start by taking you through the different stages of prostate cancer.

When a man is diagnosed with prostate cancer, how concerned should he be that his cancer may come back? There are certain factors that help predict whether he is more or less likely to have his prostate cancer recur. For patients who have had a prostatectomy, the likelihood of a rising PSA within five years is between 20-30%. If the pre-therapy PSA was less than 10, the likelihood would be 5%, but if the PSA was greater than 10, the risk jumps to 29%. Similarly, the higher the Gleason score, the higher the likelihood of recurrence. For example, the risk factor is only 8% when the Gleason score is 6 or less, but 45% when it is 7 or more. Also, men who present with bulky peripheral zone tumors have higher risk of PSA failure than men with smaller non-palpable ones.

Patients are often categorized as being at low risk, medium risk, or high risk for recurrence. For example, a patient with early stage prostate cancer (T2a with a Gleason score less than 6 and a PSA less than 10) is low risk. He has less than 25% risk of PSA failure at 5 years. A patient staged as T2b (a palpable tumor on one side of his prostate gland with a Gleason score of 7, and a PSA between 10-20) is at intermediate risk; his risk at five years ranges from 25%-50%. Finally, a patient staged at T2c (a tumor on both sides of the gland with a Gleason score of 8-10 and a PSA greater than 20) is at high risk for PSA failure at 5 years–greater than 50%.

Where are you within these risk categories? All of you should know your personal chances of PSA recurrence so that if it does recur, you already are reasonably informed about the options available to you. There are nomograms available that use postoperative data to estimate the likelihood that your prostate cancer is going to come back. For example, you can go to the internet to such a site as nomograms.com to help gain insight into just how concerned you should be in your particular circumstances.

A key to reduced risk of recurrence is early detection and the selection of the optimal therapy based on the patient's risk category. I favor a multimodality approach. For example, if a patient presents with a Gleason of 9 and a PSA of 20 (a high risk for PSA failure), I may seek to enroll him in a clinical study in which I give him chemotherapy plus hormone therapy to complement his primary therapy of surgery or radiation in an attempt to decrease the chance of his cancer coming back.

Options for High Risk Prostate Cancer

There are options for treating the high risk prostate cancer patient to decrease the chance of prostate cancer recurring after surgery or radiation therapy. They include: hormonal therapy either before or after primary therapy; radiation after surgery; and chemo-hormonal therapy after primary

therapy. There are clinical trials available here at WRAMC and the University of Maryland that may be useful. For example, after your prostate is removed, you get either hormonal therapy or hormonal therapy plus chemotherapy for two years in an attempt to preclude recurrence in high risk patients.

How about giving hormonal therapy and primary radiation therapy together? There is reason to believe that the combination might be better than just radiation alone. A large study done in Europe involved men given hormonal therapy combined with radiation therapy while others had radiation alone. The patients receiving the combined treatment did better. This is one option we can offer to a high-risk patient.

What about hormones after surgery for men in the high risk category? Suppose you have surgery and the pathologist reports the cancer has escaped the capsule. The evidence is that men receiving concomitant hormonal therapy had a much better chance after 1, 3, and 5 years of their cancer not recurring.

What if your cancer spread to your lymph nodes (Stage D1)? What can be done to reduce the risk of PSA recurrence in this case? One study of about 100 men showed that men who promptly received hormonal therapy (HT) did significantly better than those whose HT was delayed. After 7.2 years of follow-up, only 4% of those receiving immediate HT died compared to 31% of those whose HT was delayed. Another way of looking at it–only 19% of men receiving immediate HT showed progression compared to 75% of men who had delayed HT. It is clear that sooner is better for men with positive lymph nodes.

There is some interest in using chemo-hormonal therapy as an alternative to surgery and radiation. In a trial done in Britain, men with localized prostate cancer were divided into two groups. One group received hormonal therapy plus chemotherapy and the other group hormonal therapy only. The patients who got hormonal therapy plus chemotherapy were about twice as likely to have their cancers shrink, and they lived almost four years longer than the hormone-only group. This outcome has influenced the large trial being done here at Walter Reed that is attempting to determine the benefit of adding chemotherapy for men who have had their prostates removed.

In an international trial involving about 8000 patients who had received standard care (watchful waiting, radical prostatectomy, or radiotherapy), the men were randomized in a placebo-controlled, double-blind manner using the drug bicalutamide (Casodex). The idea was to see whether adding hormonal therapy to the standard therapy was beneficial. They found that those who got hormonal therapy were less likely to have their cancer progress than those who did not get the hormonal therapy. Unfortunately, it did not show any significant difference in the overall survival rate.

Evaluating PSA-Only Recurrence

What are the chances that your PSA will go up after primary therapy? About 200,000 men in the United States get diagnosed with prostate cancer each year. About two-thirds of these men have local disease for which they get some local treatment—radiation or surgery. It often comes as a great surprise to many that about 40% of these men will have a PSA recurrence after treatment. In addition, a man can be experiencing

recurrence without the accompanying rise in PSA. They likely experience some pain triggering additional testing that detects the recurrence.

Let's just say that your PSA goes up. How do you and your doctor make a decision about how to react? In assessing your options, the first step is to determine whether or not the recurrence is local or distant in nature. Then you must consider the natural course of the disease if there is no intervention. Next is a review of the available salvage therapies and their appropriateness in your situation. Finally, there is the issue of androgen deprivation (hormonal therapy) and when it should be initiated.

How does a doctor like me reach a conclusion about whether your recurred cancer is local or distant? Perhaps I ordered a bone scan or a CAT scan that were unable to locate the recurred cancer. I still need some way of deciding whether this PSA-only recurrence is local or distant. Research by Pound, *et al*., offers some guidelines. If it has been over two years since you had your primary treatment (radiation or prostatectomy), then it is more likely your recurrence is localized. If it has been less than two years, and more certainly less than six months, it is more likely the recurrence is somewhere else in your body. PSA doubling time is also an indicator. If your PSA is doubling very slowly–your PSA was 0.1, then 18 months later it was 0.2, then after another 18 months it was 0.3–it is more likely you have a localized problem. But if it is doubling relatively fast–you saw your doctor and your PSA was 1.0 and he ordered a repeat test a month later with a result of 3.0–it is more likely the recurrence is distant.

If your original cancer was staged at T3a, there is a better chance that the recurrence is localized than if it was T3b (seminal vesicle involvement). In the latter case, it is more likely beyond the prostate bed. If your Gleason score was low to start, 7 or less, the recurrence is more likely to be localized. On the other hand, a Gleason of 8 or more indicates a distant recurrence. So these are some of the considerations taken into account when you ask "What do you think is going on, Doc?"

When I see a patient with PSA-recurrence, I immediately look at his original pathology report to see what clues it offers, e.g., seminal vesicle involvement. What was his Gleason score–8 or higher? In my review of systems (ROS), I inquire about such indicators as weight loss and bone pain. I always do a rectal exam, and I may be able to detect a recurrence whether the prostate is there or not. If the patient had primary radiation therapy, the DRE is more useful as a complement to PSA monitoring. I always repeat the PSA test and check it again in 3 months if the rise is slow–and sooner if the rise is faster. I also take time to relieve patient anxiety because this is not “the end of the line.”

Men with rising PSAs often request a bone scan, but the chance of a bone scan showing anything is relatively low if the PSA is relatively low. Only when the PSA gets to about 20 do we start to see a small percentage of patients having an abnormal bone scan; by the time it rises to, let’s say 45, we start to see a significant number of abnormal bone scans.

No doubt you have heard about the ultrasensitive PSA test. In a comparison of the ultrasensitive and standard PSAs using 442 patients, 88 patients relapsed after surgery. Twenty-eight of the 88 patients (31%) initially had an ultrasensitive PSA

that showed a problem that later became evident on the standard PSA. In 42% of them, relapse was positive on both tests, while in 26% relapse was positive on the ultrasensitive and negative on the standard. So, you get more information when you test for relapse with the ultrasensitive than you do with the standard. On the other hand, do you really need to know about relapse when the PSA is that low (0.025 ng/ml)? Is it really going to make a difference? Most hospitals do not use the ultrasensitive PSA because it does not make that big an impact on what to do next.

Then there is the ProstaScint scan, a nuclear medicine scan using radioactive material that is taken up by the tissues that make PSA. Look at it as a PSA-seeking scan. ProstaScint scans are approved for patients with rising PSAs whose bone scans and CAT scans are negative. ProstaScint scans are not perfect. There is about an 89% chance that if there is something there, it will be picked up (sensitivity); but there is only a 67% chance that if there is nothing there, you will be able to say that for sure (specificity). Thus, there are a lot of people with negative ProstaScint scans who might have something, while there are many others with positive ProstaScint scans who don't have anything. That is why some physicians are wary about them. Nevertheless, the ProstaScint scan may give us some additional information when we are trying to make a decisions about whether recurrence is local recurrence or distant.

I am often asked about PET (positron emission tomography) scans. Basically they're not useful in clinical practice; they don't differentiate between prostate cancer, scarring, and BPH (benign enlarged prostate). So, I don't order PET scans on anyone.

Post RP Options

You had a radical prostatectomy and now your PSA is going up–what to do? The options are relatively straightforward. We can just follow it (observation); we can radiate the prostatic bed in the event there are a few remaining cancer cells; or we can start hormonal therapy. Observation may be appropriate if the PSA recurrence began a long time after your surgery. Let's say it has been eight years after surgery and now your PSA is starting to creep up—we may want to watch it a while longer because it is probably a very slow recurrence. The very slow velocity is suggestive of benign tissue. Your age is also an important consideration; an elderly man may prefer not to pursue further treatment under the circumstances.

Salvage radiation is often appropriate for PSA-only recurrence believed to be localized. For example, your PSA rises and it's been two-and-a-half years since your prostate was removed, your PSA rose slowly, and the number is relatively low, like 0.6. We might want to consider you for salvage radiation with the idea to again get rid of the cancer. The yardstick for success is to get your PSA back down to less than 0.2 for at least 2 years–a good sign that we've done something beneficial. Your pre-treatment information is a predictor of how you do with salvage RT. If you were diagnosed with a Gleason 9 tumor and a PSA of 30 at the time you were first seen, the chance that salvage RT is going to work is low. In fact, the likelihood that any salvage modality will be effective is similar to the likelihood that your original therapy would be effective. Putting it another way, if you had a low-risk cancer or even an intermediate-risk cancer and your cancer recurs, you are more likely to be cured by a second modality than if you had a high-risk cancer in the first place.

I am quickly showing you the results of several studies. They involved small numbers of patients who were good candidates for salvage RT. On average about 70% of such men who get salvage radiation will have their PSAs go back down to a level we'd like to achieve. Somewhere on the order of about 35% overall will actually remain what we call "biologically free of recurrence." So if you've had your prostate out and you're a good candidate for salvage radiation, you may be rendered free of cancer with a second chance.

Specific guidelines have been developed for administering salvage RT to the prostatic bed for PSA-only recurrence after surgery. It should be done when the PSA is relatively low, less than 1.5 ng/ml. The radiation dosage should be relatively high, greater than 6400 cGy. Hormonal therapy with the radiation is not recommended in this setting.

A word of caution. When you add a salvage therapy to your primary therapy, you also add to the risk of side effects. A procedure called 3D Conformal External Beam Radiotherapy employs a special computer plan to avoid radiating much of the patient's bladder and rectum. One study of this technique showed that the chance of doing well was 67% for patients who were radiated when their PSAs were less than 1.0 ng/ml. For patients who watched their PSAs rise too long before opting for salvage radiation, their chances for success were much less. Even using this improved RT technique does not avoid side effects, although they may be less severe. Studies show irritation in the rectum (20% of patients) and bladder symptoms (30% of patients). Again, when you add a second modality, you also add side effects.

Adding hormonal therapy to the salvage radiation process is another consideration. In one study, the combination did not seem to improve the chances of keeping down the PSA. So, if you take hormonal therapy for a short time while you're being radiated—and there are many hospitals that add hormonal therapy to your salvage radiation—it's not clear that it is going to make you do any better, and you still are exposed to the side effects of hormonal therapy: impotence, loss of libido, decreased bone density, and reduced quality of life.

Post Radiation Options

What if radiation was your primary therapy? First of all, the definition of "failure after radiation" is different from the definition of "failure after surgery." Radiation specialists consider failure after radiation to be three consecutive rises in PSA after nadir (lowest point). In patients who have a very low PSA after primary radiation, i.e., equal to or less than 0.5 ng/ml, there is a greater likelihood that their cancer will not recur. These are the low-risk category of patients that I mentioned earlier–low Gleason scores and low PSAs. Again, these low-risk patients are less likely for recurrence after either radiation or surgery.

If you have three consecutive PSA rises after nadir (i.e., failed radiation), what are your options? They include observation, salvage cryotherapy, salvage brachytherapy, salvage prostatectomy, and hormonal therapy. In making the decision, the patient and the doctor use the same criteria as when the patient was seen at the very outset. If the patient was in the low-risk category and seemed curable, he should be looked at in exactly the same way after failed radiation. A patient with a low PSA score and low Gleason score who was considered highly curable with radiation in the first place is the

patient who should be considered for salvage therapy. In short, it must be decided whether or not the patient is still a candidate for cure. But now, due consideration must be given to the likelihood of side effects from the salvage therapy.

Salvage Cryotherapy. Salvage cryotherapy is an option after failed radiation. The techniques are more sophisticated than they used to be. Those patients who were good candidates for curative radiation in the first place are still good candidates for curative cryotherapy. In De La Taille, *et al*., a study of salvage cryotherapy, the 43 participants who failed radiation therapy had hormonal therapy before the salvage cryotherapy. The double freeze-thaw technique was employed. After cryotherapy, the PSAs of 60% of the patients were reduced to less than 0.1. At 6 months, 79%, and at 12 months, 66% of them still had very low PSAs. There was a short follow-up, but cryotherapy should be considered after failing radiation. Let me say again, when you add a second modality, you add complications. For example, rectal pain occurs in about a quarter of men who add salvage cryotherapy; scrotal edema in 12%; incontinence and infection in 9%; and obstruction, urethral stricture, and hematuria in 5%.

Salvage Brachytherapy. Salvage brachytherapy is another option. In one study of 49 patients with proven localized recurrence after external beam radiation, the salvage brachytherapy numbers look good–about 30% of the patients had no biological evidence of prostate cancer and their PSAs had not gone up in 5 years. Let me add here that any salvage option is more complicated than original therapy. If you are a candidate for a salvage option, you need to place yourself in the hands of an institution whose staff has considerable experience in your selected salvage option.

Radical Prostatectomy. Radical prostatectomy is possible after failed radiation. If you were a candidate for an RP in the first place, but chose radiation, you could choose a salvage prostatectomy if you are still in good physical condition. Experience shows that disease free rates at five years range from 23-88% with 60% being representative. The incontinence rate is very high, ranging from 40-100%. The impotence rate is not encouraging, either–90+%. In addition, there is also the chance of rectal injury. Many institutions with experienced urologists usually offer the salvage RP as part of a salvage study as opposed to a routine procedure.

Hormonal Therapy. Let's turn to hormonal therapy for PSA-only recurrence. Your doctor may determine you are not a candidate for local salvage therapy; perhaps your PSA is going up fast and you relatively recently had surgery or radiation as primary therapy; now your doctor is recommending hormonal therapy. Alternatively, you may have choices but select hormonal therapy because you find other salvage options unappealing. There is no compelling information to support early hormonal treatment of PSA-only recurrence as a way to improve survival. Many men delay initiating hormonal therapy, even though they think the cancer is probably present. If you do select hormonal therapy for PSA-only recurrence, there are several variations: the traditional hormonal monotherapy (an LHRH agonist like Lupron or a similar drug); combined hormonal therapy; non-traditional oral hormonal therapies; or intermittent hormonal therapy.

At this point, let me give you an idea of the natural history of prostate cancer to illustrate

the time track patients may be on. Pound *et al.,* followed 1,997 men who had radical prostatectomies. Eventually 15% of these men had rising PSAs, and of these, 34% experienced metastasis. The researchers found that it took eight years from the time of the PSA rise to the documented spread of their cancer. They also found that after metastasis, it was about 5 more years until 14% succumbed to their cancer. This reinforces my earlier comment that there is no need for panic if you experience PSA-only recurrence. Depending on the velocity of the rise, there is ample time to resort to salvage therapies.

Here is a not uncommon scenario. You may or may not find yourself in this setting. You had a prostatectomy at age 59. Three years later at age 62, your PSA has risen to 0.5 ng/ml. Eight years later, at 70, you are still otherwise healthy, but your PSA is now 15 ng/ml, and you have a positive bone scan. At 75, still otherwise healthy, you die of prostate cancer. The critical decision in this scenario is at what point should we intervene, and with what therapy, to change this natural time course. Most urologists and oncologists will say, "Before we do something secondarily and put you through therapies that can affect you and your quality of life, we want to be absolutely certain it is the right course." A very interesting study done by Amling, *et al*., gives some insight into when to intervene in PSA-only recurrence (Dr. Amling is an active duty military urologist associated with your Center for Prostate Disease Research). The researchers followed almost 3,000 patients who had radical prostatectomies. They concluded that a PSA cut-point of less than 0.4 ng/ml is the best level at which to consider treatment for PSA-only recurrence.

I previously raised the question about earlier or later intervention with hormonal therapy and its effect on survival. Dr. Judd Moul and others at the Center for Prostate Disease Research (CPDR) followed 343 patients who had radical prostatectomies and who were at high risk for PSA recurrence—Gleason scores greater than 7 or PSA doubling times of less than 12 months. Their general conclusion was that early intervention (at PSA equal to or less than 5 ng/ml) offered more benefit than later intervention (at PSA greater than 5 ng/ml) or no intervention at all. On the other hand, for patients at low risk of PSA recurrence (low PSAs and Gleason scores) who have a really slow rise in their PSAs, it hasn't been shown that they will benefit from starting them on hormonal therapy. No doubt this is a controversial subject. Some experts hold that there is insufficient evidence that starting hormonal therapy before metastatic disease is going to result in increased survival.

In short, PSA-only recurrence is a common condition. Early rises in PSA, rapid PSA doubling time, high-grade disease and seminal vesicle invasion are all indicators of advanced systemic disease. Such patients may benefit from early intervention with hormonal therapy, or they may benefit from going on a clinical trial that is even more aggressive. In the case of localized PSA-only recurrence, whatever salvage therapy is selected, it needs to be done early–before the PSA is greater than 1.5 ng/ml. So, if your PSA is slowly rising, it's been two or three years since your surgery and you are considering a salvage therapy, do it sooner rather than later. Finally, hormonal therapy is the mainstay of treatment for PSA-only recurrence if you are not a candidate for local salvage therapy.

Metastatic Disease

Now I want to touch on a few related topics. The first is metastatic disease. When I was in training, they said there was no reason to start hormonal therapy until someone had symptoms. That is no longer the case. Patients with metastatic disease should get treatment immediately. A study done in Britain found was that such men who got early hormonal therapy were less likely to break bones, they were less likely to have complications with their cancers—ureteric obstruction, kidney damage, extraskeletal metastases—and they were less likely to die of their prostate cancer. So we now know that if cancer is proven to be somewhere, like in your bones, that is not considered an early disease you want to watch. You need to start on treatment.

Intermittent Hormonal Therapy

Intermittent hormonal therapy involves the initiation of hormonal therapy and its continuance until some benchmark is reached, e.g., a reduced, sustainable PSA. Hormonal therapy is resumed in the event the PSA rises again. The idea is that the intermittent exposure of prostate cancer cells to androgen deprivation will delay progression to the androgen insensitive stage. If you decide on this type of therapy, you should know that it is uncertain whether intermittent hormonal therapy can be considered the equivalent to continuous hormonal therapy. We do know that by using hormonal therapy in addition to something like radiation, we may be able to cure your cancer. But if we were using hormonal therapy for metastasized cancer and we go on and off the therapy, we have no information that tells us that the effect is the same as continuous therapy. Many urologists and oncologists believe it should be done only in a clinical study, and there are several clinical studies that address intermittent hormonal therapy. In the meantime, intermittent hormomal therapy must be considered experimental.

Hormone Refractory Disease

Hormone refractory disease occurs when the cancer cells no longer need androgen to grow. The hormonal therapy becomes ineffective and the androgen-independent cells take over. If you are on hormonal therapy and your PSA goes up, immediately see an oncologist who treats refractory disease. There are several second-line therapies that may benefit you. Two or three different second-line hormonal therapies that sometimes can bring your PSA back down include drugs like ketoconazole, diethylstilbesterol (called "DES"), and Casodex. These therapies may bring your PSA down, keeping your disease under control for maybe six months, maybe a year, or maybe even longer. I have many patients—even though their PSAs went up while taking Lupron—whom I put on ketoconazole, and their disease has been back under control for two or three years. So, if you become hormone refractory, there are multiple secondary hormonal therapy options. I have been dealing with them for years.

Chemotherapy

The newest development in dealing with recurring prostate cancer is chemotherapy. You may be aware of two significant studies reported at the recent American Society of Clinical Oncology meeting. The studies showed for the first time that chemotherapy improved survival for men with hormone refractory prostate cancer. We have been studying this for years, but only recently

were we able to demonstrate that we could actually help men live longer by giving them chemotherapy when their disease becomes hormone refractory. We knew that men with widespread hormone refractory disease live about a year. The drug that made the breakthrough is called Taxotere (docetaxel), a taxane-based chemotherapy that is clearly active in prostate cancer. Early phase studies showed a trend toward improved median survival; men taking this chemotherapy were living closer to two years. Oncologists consider this near two-year survival rate to be a big deal. So they did the Phase III study comparing docetaxel to mitoxantrone, a standard drug. It showed that docetaxel increased survival by about two-and-one-half months. This is important scientific news. Patients initially showed a lot of interest, but they lost some enthusiasm when they understood the improvement in survival was only about two-and-one-half months. So we still have a long way to go. Nevertheless, for the first time we have a chemotherapy that improves survival.

Skeletal-Related Events

If you have hormone refractory disease or if you are worried about getting it, you should be aware of the drug Zometa. Zometa is not a chemotherapy drug; it is a so-called bisphosphonate that prevents the breakdown of bone. It is given intravenously. Zometa was FDA-approved in 2002 to prevent skeletal-related events (e.g., breaking bones and spinal cord compression) in men who have prostate cancer with osteoblastic metastases. Zometa is a relatively safe drug with few side effects. It is becoming standard to give Zometa with chemotherapy or second-line hormonal therapy to keep metastatic, hormone-refractory men from having skeletal-related events. There is every reason to believe that Zometa also will benefit men who are on hormonal therapy and have metastatic disease in their bones but who are not yet hormone refractory. A study in that regard is under way.

It is well-known that hormonal therapy causes bones to get thinner. Thinner bones break more easily. So, if you're on hormonal therapy: (1) you should have a baseline bone mineral density scan; (2) you should be taking Vitamin D and calcium supplements; and (3) if your bones are getting thinner, you should be on something additional, perhaps an oral bisphosphonate like Fosamax. Again, don't overlook Zometa. At present, it is only approved for men with hormonal refractory disease with cancer in their bones. But many doctors recommend its off-label use for men whose bones are getting thin.

Conclusion

In conclusion, I want to emphasize that the treatment of prostate cancer is ever-changing as are the available therapeutic options, depending on where you are in the course of your disease. It is very important to individualize your treatment plans. No two men are alike. Never mind what the other six guys need. Although you're bonded together in your support group and you're good friends, your options are different from the person sitting next to you. And remember, treating prostate cancer requires a team approach. Many of the therapies mentioned tonight are offered by a variety of specialists–radiation therapists, oncologists, and urologists. If you are faced with a recurrence, consider seeing the several specialists who treat prostate cancer in order to get the widest range of options to treat your disease. It is great being back at WRAMC tonight. Thank you for inviting me.

Dr. Hudak Recognized

Jane L. Hudak, RN, DNSc, Patient Educator/Counselor at the Center for Prostate Disease Research, recently received a citation for distinguished service from US TOO International, the largest national prostate cancer education and support organization. US TOO recognized Dr. Hudak's sustained distinguished service to the organization and its Walter Reed Army Medical Center (WRAMC) Chapter. The award specifically noted Dr. Hudak's "expert and empathetic support of men diagnosed with prostate cancer and their families." It also cited her role in the expansion of the chapter's educational and outreach activities, as well as the development of a widely used, specialized prostate cancer lending library for the chapter and its members. The US TOO citation was presented to Dr. Hudak by Dr. David G. McLeod, Director, Center for Prostate Disease Research, at a recent meeting of the WRAMC US TOO Chapter.

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♦ SPEAKER ♦

JASON D. ENGEL, MD
CENTER FOR ROBOTIC SURGERY
GEORGE WASHINGTON UNIVERSITY HOSPITAL

♦ TOPIC ♦

"New Techniques: The da Vinci Robotic Surgical System"