Us TOO® PROSTATE CANCER EDUCATION & SUPPORT

HOTSHEET

FEBRUARY 2015

TWO PROSTATE CANCER TESTS 'NOT CLINICALLY USEFUL,' SAYS NICE

Two tests designed to help identify prostate cancer in men with negative or inconclusive prostate biopsy results do not improve diagnosis enough to be recommended for clinical practice, says the United Kingdom (UK)'s healthcare watchdog, the National Institute for Health and Care Excellence (NICE).

In draft diagnostics guidance issued on December 17, NICE recommends that the Progensa® prostate cancer antigen 3 (PCA3) assay (Hologic) and the Prostate Health Index (PHI®) (Beckman Coulter) should not be used in the National Health Service in England.

PCA3 and PHI are both in vitro diagnostic tests for use in patients suspected of having prostate cancer who have negative or inconclusive findings on transrectal ultrasound prostate biopsy; these tests are used to determine the need for a second biopsy.

The appraisal was undertaken in the belief that the PCA3 or PHI may avoid second biopsies and associated complications by identifying patients unlikely to have a positive biopsy result and, thus, prostate cancer. However, the draft guidance says that adding either of these tests to clinical assessment plus MRI is unlikely to improve diagnostic accuracy in clinical practice.

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SURVEILLANCE MAY BE SAFEST OPTION FOR LOW–RISK PROSTATE CANCER

Among men whose low–risk prostate cancer was managed with active surveillance for up to 15 years, just 1.5% died of the cancer, according to new data from an ongoing Canadian study. That result is similar to outcomes in men whose cancers are treated immediately, the authors write.

In the Canadian trial, 993 men with low– or intermediate–risk prostate cancers were enrolled in an active surveillance protocol between 1995 and 2013. By now, more than 200 of them have been observed for more than 10 years and 50 for more than 15 years.

"This is the third time we've published the key results of our long–term surveillance cohort," said lead author Dr. Laurence Klotz of Sunnybrook Health Sciences Center in Toronto. As of now, only 27% of the men have been treated for their cancers. And while 149 of the men have died, only 15 died from prostate cancer, the researchers reported online December 15th in the *Journal of Clinical Oncology*.

All the men who died from the cancer had metastatic disease. Another 13 men had metastases but died from causes other than prostate cancer. In all, less than 3% developed metastatic cancer, which is similar to the rate of metastases

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LOWER DEATH RATES IN MEN WITH PROSTATE CANCER WHO EXERCISE

Yet another study is confirming the benefits of physical activity following the diagnosis of cancer, this time of prostate cancer, on all–cause and prostate–specific survival, Swedish researchers report. The study was published online December 19 in *Cancer Epidemiology, Biomarkers & Prevention*.

"Being physically active has many positive effects on health, and now we can see that it has specific effects on survival among prostate cancer patients as well," Stephanie Bonn, MSc, Karolinska Institute, Stockholm, Sweden, told *Medscape Medical News*.

"Since a man's physical activity level is something he himself can change, there is great potential for men to improve their own survival by being physically active and we believe that physical activity after a prostate cancer diagnosis is beneficial for survival regardless of the patient's activity level before the diagnosis," she said.

Investigators used data from 4,623 men involved in the National Prostate Cancer Register of Sweden Follow-up Study, a nationwide cohort study of men with localized prostate cancer who were alive in 2007. Men had been diagnosed with localized prostate cancer between 1997 and 2002 and were followed up until

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DIETHYLSTILBOESTROL (1 MG) IN THE MANAGEMENT OF CASTRATION-RESISTANT PROSTATE CANCER

Turo R, Tan K, Thygesen H, et al

Urol Int 21 October 2014; Epub

Objective: To investigate the efficacy of diethylstilboestrol (DES) in patients with advanced prostate cancer refractory to androgen suppression.

Methods: This retrospective study comprises 194 patients with prostate cancer treated with DES (1 mg daily) between 1976 and 2010. Study outcome parameters included demographic data, tumour characteristics, treatment history, prostate-specific antigen (PSA) responses, radiologic studies, adverse events and overall survival.

Results: At initiation of oestrogen therapy the mean patient age was 69 years (range: 48-89) and the median PSA was 96 ng/ml (range: 1.9-9,500). The median duration of prior prostate cancer treatment was 29 months (range: 1-365). DES was the second-line treatment in 58 patients and the third/fourth–line therapy in 136 men. A formal (≥50%) PSA response was observed in 95 patients (48.9%) and the median time to progression (TTP) was 250 days (95% CI, 180-360) for this group. An additional 62 patients (31.9%) had a partial PSA response with a median TTP of 150 days (95% CI, 92-180). Thirty–seven patients (19.1%) did not have a PSA response and the median TTP was 90 days (95% CI, 90-97). The median overall survival from the start of oestrogen therapy for the entire cohort was 576 days (95% CI, 482-690). The median overall survival of patients who had a formal (≥50%), partial (< 50%) and no PSA response was 756 (95% CI, 670-1,429), 428 (95% CI, 340-630) and 329 (95% CI, 287-510) days, respectively. Thirty–nine patients (20.1%) were still alive at the end of the study. No treatment–related deaths occurred.

Conclusions: In the age of chemotherapy this study highlights the efficacy of oestrogen therapy in castration-refractory prostate cancer. The optimal point in the therapeutic pathway at which DES should be prescribed remains to be established.

STEREOTACTIC RADIOTHERAPY FOR ISOLATED NODAL RECURRENCE OF PROSTATE CANCER

Detti B, Bonomo P, Masi L, et al

World J Urol 24 October 2014; Epub

Purpose: To report a clinical experience in stereotactic body radiation therapy (SBRT) for isolated nodal metastases from prostate cancer.

Materials and Methods: Between November 2011 and December 2013, 30 patients (39 lesions) were treated with SBRT, delivered using Cyberknife, for recurrent prostate cancer with isolated nodal metastases. Prescribed doses and schedules of fractionation varied, ranging from 24 Gy in one fraction to 36 Gy in three fractions. Most commonly used schedules were 30 Gy in three fractions and 36 in Gy in three fractions on alternating days. Biochemical response, acute and late toxicity were analyzed.

Results: At a median follow-up of 12 months (range 2-24.9), a significant reduction of PSA was observed in 24 cases, while PSA was stable in one case and raised in nine cases. At the time of analysis, among the 30 patients treated, two were dead for systemic disease; 12 patients experienced a relapse of disease in other sites. Sixteen patients were still free of disease. In 24 cases, imaging evaluation three months after treatment was available. No in-field recurrence was detected. SBRT was well tolerated: One patient experienced G2 acute genitourinary toxicity. Late toxicity was evaluated in patients with more than six months of follow-up, and only one complained G1 proctitis. We did not observe any acute or late severe toxicity (≥G3).

Conclusions: Our experience shows that SBRT for isolated nodal relapse from prostate cancer is a safe treatment, with promising results in terms of efficacy.

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SURVEILLANCE MAY BE BEST

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in another study of men with low-risk disease who were treated immediately, according to Dr. Matthew R. Cooperberg of the University of California, San Francisco.

"In recent years, active surveillance has evolved from an experimental protocol to a broadly accepted – in fact, preferred –management strategy for men diagnosed with low–risk prostate cancer," he wrote in an editorial in the Journal.

"Twenty years ago, treating every prostate cancer patient was the norm," Klotz told Reuters Health by phone. "Over the years this has evolved. This whole approach is one of evolution and we can do better than that," he said.

In this group of low–risk cancers, about 25% turned out to be "wolves in sheep's clothing," he said. "Those that metastasized weren't low–grade disease that spread, rather they were hidden higher–grade disease that was missed," Klotz said. "But today, magnetic resonance imaging can detect many of the more dangerous cancers that may have missed with a biopsy 20 years ago.

"Men in the study who died from prostate cancer succumbed about 15 years after diagnosis, usually in their 80s," he noted. "It really looks like (active surveillance) is a safe strategy for the management of probably 40% to 50% of newly diagnosed prostate cancer patients," he said.

"Overtreating prostate cancers that would not ultimately be fatal can lead to incontinence, erectile dysfunction and other problems, he continued. "That's why I think this approach is so important, if you can significantly reduce overtreatment but you still have the benefit of screening.

"Active surveillance has been widely embraced in Canada and has been somewhat slower to catch on in the US, but is becoming more common," Klotz said. "The bottom line is, it's catching on and I also think the role of MRI will provide further reassurance for doctors and patients," he concluded.

Reuters Health, 22 December 2014

DOC MOYAD'S WHAT WORKS & WHAT IS WORTHLESS COLUMN, ALSO KNOWN AS "NO BOGUS SCIENCE" COLUMN

"TV Shows that Cover Health Advice Are Often Wrong!"

Mark A. Moyad, MD, MPH, Univ. of Michigan Medical Center, Dept. of Urology

Editor's Note: Us TOO has invited certain physicians and others to provide information and commentary for the *HotSheet* to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and is not necessarily those of Us TOO International.

Bottom Line:

A recent study of the *Doctor Oz Show* and *The Doctors* found that often their advice is not accurate and conflict of interest is revealed less than 1% of the time![1] Say it ain't so!

Look, I was on Dr. Oz (it was a lifestyle piece and I was really good – just ask me and no one else) and I think he and other health shows have provided some valuable advice (politically correct statement and a disclaimer all in one – way to go Moyad). However, apparently these shows have also had some very bad moments and I do not disagree with that! (Ahhh, the Moyad opinion comes to the surface).

A fabulous group of Canadian researchers got together not to drink beer and fight and play hockey but rather to evaluate the accuracy of the *Dr. Oz Show* and *The Doctors* and what they found was a little scary! They randomly selected 40 episodes and reviewed a total of 80 recommendations from both shows. There was evidence to support a claim less than half of the time and over 50% of the time there was no evidence or contradictory evidence. This was for the *Dr. Oz Show – The Doctors Show* did only a little better than this. However, the scary part was that less than 1% of the recommendations included information on the conflicts of interest.[1]

The researchers concluded their study by suggesting that consumers need to be skeptical about recommendations on these shows! Ouch! Bam! Yikes! Scary! Zowie (Is that a word)! I like to use exclamation points! Regardless, there are many lifestyle tips on these shows that I believe help a lot of folks! However, when these shows begin to recommend dietary supplements or some drugs and procedures, they have some inaccurate information. I think all of this can be cleaned up but will it keep their audience? In other words, I believe there are many people that want to believe in magic potions and miracle weight loss products. And, part of what is also driving this criticism is that I believe there are a lot of jealous doctors that would like to have their own show.

Still, these TV shows need to do a better job of referring to well–done research and if you think about it for a second, when it comes to surgery or taking pills, how can you decide what is right for you in a few-minute segment? That is insane! I like *Doctor Oz* and *The Doctors* (they are also so good looking and dreamy) just like I like some reality TV shows but I am not about to get prostate advice from these folks. Lights, camera, and inaction! That is my motto!

Reference:

1. Korownyk C, Kolber MR, McCormack J, et al. Televised medical talk shows—what they recommend and the evidence to support their recommendations: a prospective observational study. BMJ 17 December 2014, Epub ahead of print.

US TOO LEADERSHIP TEAM IN PLACE FOR 2015

A new roster of Us TOO leadership was established at the December 2014 board meeting as thanks and appreciation were extended to all current and former board members. Having completed their terms in office, vice hairman Jeff Mills and board member cDexter C. Rumsey, III, moved off the board of directors as it transitioned to a new leadership team, which is charged with making the organization even stronger and more vital in 2015, which marks the 25th anniversary of Us TOO.

Jerry Deans assumes the office of vice chairman and joins continuing executive committee members Chairman Jim Rieder, Treasurer C. Todd Ahrens and Secretary William Seidel. Continuing Us TOO board members Fred Allen, Tom Cvikota, Jim Hammack, Jerry Hardy,

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RETROPUBIC, LAPAROSCOPIC AND MINI-LAPAROSCOPIC RADICAL PROSTATECTOMY: A PROSPECTIVE ASSESSMENT OF PATIENT SCAR SATISFACTION

Quattrone C, Cicione A, Oliveira C, et al

World J Urol 26 October 2014; Epub

Purpose: To compare patient scar satisfaction after retropubic, standard laparoscopic, mini-laparoscopic (ML) and open radical prostatectomy (RP).

Methods: Patients undergoing RP for a diagnosis of localized prostate cancer at a single academic hospital between September 2012 and December 2013 were enrolled in this prospective nonrandomized study. The patients were included in three study arms: open surgery, VLP and ML. A skin stapler was used for surgical wound closure in all cases. Demographic and main surgical outcomes, including perioperative complications, were analyzed. Surgical scar satisfaction was measured using the Patient and Observer Scar Assessment Questionnaire (POSAS) and the two Body Image Questionnaire (BIQ) scales, respectively, recorded at skin clips removal and either at 6 months after surgery.

Results: Overall, 32 patients were enrolled and completed the 6 month of follow-up. At clips removal, laparoscopic approaches offered better scar result than open surgery according to the POSAS. However, at 6 months, no differences were detected between VLP and open, whereas ML was still associated with a better scar outcome ($p = 0.001$). This finding was also confirmed by both BIQ scales, including the body image score (ML 9.8 ± 1.69, open 15.73 ± 3.47, VLP 13.27 ± 3.64; $p = 0.001$) and the cosmetic score (ML 16.6 ± 4.12, open 10 ± 1.9, LP 12.91 ± 3.59; $p = 0.001$). Small sample size and lack of randomization represent the main limitations of this study.

Conclusions: ML RP offers a better cosmetic outcome when compared to both open and standard laparoscopic RP, representing a step toward minimal surgical scar. The impact of scar outcome on RP patients' quality of life remains to be determined.

TESTS NOT CLINICALLY USEFUL SAYS NICE *(Continued from page 1)*

"Prostate biopsies are associated with discomfort and pain, as well as side effects including bleeding, problems with catheterization and possible infections," Carole Longson, PhD, NICE Health Technology Evaluation Centre director, commented in a statement. "These tests would be of value if they were able to improve diagnostic certainty because it would reduce the number of prostate biopsies patients had to have, reducing patients' anxiety," she continued.

However, the committee noted from the evidence that, although there were some improvements in diagnostic performance when PCA3 or PHI was added to clinical assessment alone, these improvements were very small.

The PCA3 assay is an in vitro nucleic acid amplification test for determining levels of PCA3 RNA in urine. The urine sample is obtained after digital rectal examination, which releases prostate cells and RNA into the urinary tract. The PCA3 assay was approved for use in Europe in 2006, and received US Food and Drug Administration approval in 2012, based on a study involving 495 men at 14 clinical sites that indicated the assay had a negative predictive value for prostate cancer of 90%.

A further study conducted in 233 men with persistently elevated serum PSA levels and at least one previous negative biopsy result suggested that the PCA3 assay may help reduce the number of biopsies performed in men suspected of having prostate cancer. The assay performed significantly better than serum PSA in predicting the outcome of prostate biopsies.

Furthermore, an analysis of 1,072 men from the REDUCE (REduction by DUasteride of prostate Cancer Events) study suggested that higher PCA3 scores not only predicted a positive biopsy result but was also associated with a higher biopsy Gleason score. Further improvements in the ability of the PCA3 assay to identify men with prostate cancer have been reported when used in combination with the TMPRSS2:ERG gene fusion, and with a panel of biomarkers.

In contrast, the PHI is an in vitro diagnostic multivariate index assay that combines three blood serum PSA immunoassays – PSA, free PSA, and p2PSA – into a single calculation (p2PSA/free PSA) × %total PSA. The test is simple and inexpensive and has performed better than conventional serum PSA and free PSA levels in several studies for predicting overall and high–grade prostate cancer.

For the current draft NICE guidance, researchers from the External Assessment Group conducted three systematic reviews of the evidence, identifying six studies that reported the analytical validity and 31 that reported the clinical validity of the tests. No studies that reported the clinical validity of the tests were identified.

In addition, the group conducted a systematic review of the existing economic analyses of the PCA3 and PHI tests. Because no published economic studies met the inclusion criteria, the group designed their own de novo economic model designed to assess the cost effectiveness of the tests.

After reviewing the available evidence, the guidance committee considered whether more research into the two assays was advisable. Noting that any potential improvements to the tests would be small, the guidance says: "If the potential benefits of using the PCA3 assay and the PHI were realized, they were unlikely to be sufficiently large to offset the costs of the test and make a substantial difference to the number of people having a second biopsy unnecessarily."

Medscape Medical News, 22 December 2014

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LOWER DEATH RATES IN MEN WITH PROSTATE CANCER WHO EXERCISE *(Continued from page 1)*

2012. Mean age at diagnosis was 63.1 years, and most men included in the analysis had a body mass index between 25 and 30 kg/m^2.

Participants were asked to report how much time they spent walking or cycling, exercising, or carrying out household work after the diagnosis of prostate cancer. Each activity was assigned a metabolic equivalent (MET) level based on MET values specified in the *Compendium of Physical Activities*.

As Bonn explained, a MET represents the ratio between the energy expenditure from a specific activity and the energy expenditure from basal metabolism. For example, an activity with a MET of one (sitting still) does not result in any increased energy expenditure compared with basal metabolism, whereas an activity with a MET of two (standing) results in twice the energy expenditure. "The higher the MET value of an activity, the higher the energy expended when performing that activity," Bonn added.

During follow-up, investigators identified 561 deaths from any cause and 194 deaths from prostate cancer. Men who walked or cycled for 20 minutes a day or more had a 30% lower risk for all-cause mortality and a 39% decreased risk for prostate cancer–specific mortality compared with men who walked or cycled less than 20 minutes a day, investigators report. For those exercising one or more hours a week, all-cause mortality was reduced by 26% and prostate cancer–specific mortality by 32% compared with men who reported exercising less than one hour a week.

After considering all time spent walking, cycling, exercising, and doing household work, researchers found that all-cause mortality was 37% lower while prostate cancer-specific mortality was 22% lower for men who had a total MET of five or more hours a day compared with those who had a total MET of less than five hours a day.

Hazard Ratios after Multivariable Adjustment for Overall and Prostate Cancer–Specific Mortality

Activity after Prostate Cancer Diagnosis	Overall Mortality	Prostate Cancer-Specific Survival
Walking/cycling <20 vs. ≥ 20 minutes/day	0.70	0.61
Household work < vs. ≥ 1 hour/day	0.71	0.86
Exercise < 1 vs. ≥ 1 hour/week	0.74	0.68

"I would recommend physicians advise men to follow the current recommendations for physical activity that are available, and to advise them to be as active as is possible for them to be," Bonn said.

"They need to find an activity that is enjoyable and remember that any physical activity is better than none and is likely to have positive health effects," she added.

Medscape Medical News, 23 December 2014

US TOO LEADERSHIP

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Keith Hoffman, David Lubaroff and Jim Naddeo are joined by newly-elected board members Peter Friend, Chad Little and Jim Schraidt.

Hailing from Deerfield, IL, Peter Friend is a prostate cancer survivor and works as a director with The Bensman Group where he helps client organizations improve productivity and reduce costs through wellness and population health management. His background also includes substantial experience as a C-suite executive with major hospitals/ health systems and author of several published books and articles.

Chad J. Little from La Mesa, CA, became an impassioned advocate for increasing awareness for prostate cancer after his father was diagnosed with the disease in 2006. Having developed exceptional business and project management skills throughout his career, he currently is the strategic sales project manager/account manager vice president with Union Bank/Washington Mutual/Reunion Mortgage.

After a prostatectomy in 2010 at age 58, Jim Schraidt from Riverside, IL, began attending the Us TOO Gilda's Club Chicago support group and is now the leader of the group. Jim is a partner at Chicago law firm Scott & Kraus with 35 years in law with a focus on the finance sector, and experience with legislative advocacy as general counsel to the Illinois Development Finance Authority.

We are continuing to accept applications to fill one existing open board seat. Interested candidates are invited to contact Tom Kirk at tomk@ustoo.org.

A PHASE II TRIAL EVALUATING THE EFFICACY AND SAFETY OF EFAVIRENZ IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Houédé N, Pulido M, Mourey L, et al

Oncologist 29 October 2014, Epub ahead of print

Background: Preclinical studies demonstrated that non–nucleoside reverse transcriptase inhibitors used for the treatment of HIV could antagonize tumor development. This led us to assess the efficacy of efavirenz (EFZ) in patients with metastatic castration–resistant prostate cancer (mCRPC) in a multicenter phase II study.

Methods: We used a Simon two-stage design and a three–month PSA nonprogression rate of 40% as a primary objective. Patients received 600 mg EFZ daily with the possibility of a dose increase in case of PSA progression. Exploratory analyses included pharmacokinetics of EFZ plasma concentrations and correlations with clinical outcomes.

Results: Among 53 assessable patients, we observed 15 instances of PSA nonprogression at three months, corresponding to a nonprogression rate of 28.3% (95% confidence interval: 16.8% -42.3%). The exploratory analysis revealed that for the seven patients in whom optimal plasma concentration of

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MORE EVIDENCE OF HARM FROM SELENIUM IN PROSTATE CANCER

A new analysis has found that men diagnosed with nonmetastatic prostate cancer who consumed more than 140 micrograms (μg) a day of supplemental selenium had over a two–and–a-half–fold excess risk for death from prostate cancer compared with nonsupplement users. The new finding comes from the Health Professionals Follow-Up study (HPFS) and was published online December 12, 2014, in the *Journal of the National Cancer Institute*.

"There is no evidence for benefit from taking selenium after a prostate cancer diagnosis and now we have evidence for harm," lead author Stacey Kenfield, ScD, University of California, San Francisco, told *Medscape Medical News*. "Based on these findings, prostate cancer patients should avoid selenium supplements," she said, "although further research evaluating high–dose selenium intake is needed to confirm our results and inform clinical guidelines for prostate cancer survivors."

Dr. Kenfield and colleagues prospectively followed 4,459 men initially diagnosed with nonmetastatic prostate cancer from 1988 through to 2010. Participants completed detailed information on the use and dosage of supplements, including multivitamins and individual vitamins and minerals, every two years beginning in 1986.

Total selenium supplement intake was calculated as the sum from multivitamins and selenium supplements. Men were categorized according to how much selenium they were taking: less than 80 μg daily, 80 to 130 μg daily, between 140 and 250μg daily, and 260 μg daily or more. There was also a "don't know" category.

During a median follow-up of 8.9 years, investigators documented 965 deaths, 23.4% of them due to prostate cancer and 27.7% due to cardiovascular disease. "Compared with nonusers, selenium supplement users had an increased risk of prostate cancer mortality," the investigators report.

On the basis of multivariable analyses, men who consumed the lowest amount of selenium (1 to 24 μg/day) after being diagnosed with prostate cancer had an 18% higher risk for prostate cancer mortality compared with nonusers (hazard ratio, 1.18). This risk increased by 33% in men who consumed between 25 and 139 μg of supplemental selenium a day (HR, 1.33) and by 60% among men who consumed 140 μg of supplemental selenium or more per day (HR, 2.60).

Investigators also analyzed the risk for biochemical recurrence of prostate cancer and the amount of selenium supplementation consumed. On the basis of an analysis of 3,718 men followed for a median of 7.8 years, they observed no statistically significant association between selenium supplementation after prostate cancer diagnosis and the risk for biochemical recurrence.

On the other hand, there was a modest 12% inverse association between selenium supplementation and the risk for overall mortality (HR, 0.88) among men who took 140 μg of a selenium supplement or more per day compared with those who didn't use supplements.

Although not a statistically significant finding, investigators also noted that men using the highest doses of selenium supplements after prostate cancer diagnosis had a statistically significant 36% decreased risk for cardiovascular mortality (HR, 0.64; *P* for trend = 0.38). However, researchers also point out that these men were generally healthier. At diagnosis, men who consumed 140 μg of selenium supplements or more per day did more vigorous physical activity, smoked less, used other supplements, and were more likely to have clinical T1 stage cancers, although use did not vary by biopsy Gleason score, as investigators observe.

Asked to comment on the study, epidemiologist Theodore Brasky, PhD, from the Ohio State University College of Medicine, Columbus, told *Medscape Medical News* that there are two sides to this story: the relation between selenium intake and prostate cancer occurrence and the relation between selenium intake and prostate cancer survival among men who have already been diagnosed with prostate cancer.

"In the SELECT trial (Selenium and Vitamin E Cancer Prevention Trial), which was an incredibly large trial of over 35,000 men, investigators found no effect on prostate cancer risk from sele-

(Continued on page 8)

ELUCIDATING IMMUNOLOGIC MECHANISMS OF PROSTVAC CANCER IMMUNOTHERAPY

Mandl S, Rountree R, Dela Cruz T, et al

J Immunother Cancer 2014;2(1):34

Background: PROSTVAC®, an active immunotherapy currently studied for the treatment of metastatic castration–resistant prostate cancer (mCRPC), consists of a heterologous prime-boost regimen with two different poxvirus–based vectors to provoke productive immune response against PSA as the target tumor antigen.

A Phase 2 study of PROSTVAC immunotherapy showed significantly improved median overall survival by 8.5 months and is currently being validated in a global Phase 3 study (PROSPECT). Here, preclinical models were explored to investigate the mechanism of action and immune signatures of anti–tumor efficacy with PROSTVAC immunotherapy with the goal to identify potential immune correlates of clinical benefit.

Methods: PROSTVAC-induced immune responses and anti–tumor efficacy were studied in male BALB/c mice. Functionality of the induced T cell response was characterized by interferon–gamma (IFNγ) ELISPOT, cytotoxic degranulation, multi-cytokine intracellular staining, and in vivo T cell depletion. Tumor infiltrating lymphocytes (TILs) were evaluated phenotypically by flow cytometry.

Results: The heterologous prime-boost regimen of the two PROSTVAC vectors significantly enhanced the magnitude and quality of activated PSA–specific CD4 and CD8 T cell responses compared to homologous, single vector regimens. PROSTVAC–activated CD4 and CD8 T cells were highly functional as evidenced by expression of activation markers, production of multiple cytokines, and amplified cytotoxic T cell activity. Importantly, PROSTVAC immunotherapy resulted in significant antitumor efficacy in a transplantable prostate cancer mouse model. Antigen-spreading occurred in PROSTVAC–treated animals that rejected PSA-expressing tumors, as shown by subsequent rejection of PSA–negative tumors. In vivo CD4 and CD8 depletion re-

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DOCTOR CHODAK'S BOTTOM LINE *(Ref Key: article #, page #, column #)*

Gerald Chodak, MD, Author, *Winning the Battle Against Prostate Cancer*, Second Edition http://www.prostatevideos.com/

Editor's Note: Us TOO has invited certain physicians and others to provide information and commentary for the *HotSheet* to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and is not necessarily those of Us TOO International.

a1p1c1 Genetic testing is working its way into prostate cancer management. Two of these tests, PHI and PCA3 are intended to help decide if a man should have a repeat biopsy after one is negative. Both provide a numerical result and the recommendation is to undergo a biopsy if a certain value is exceeded. One of the limitations is that neither test provides a definite yes or no answer. Instead they provide a probability or percent odds of finding cancer on the second biopsy. Even at the lowest values, some men have a cancer that would go undetected if a biopsy is not done. Although both tests are approved in the US, the British organization NICE reviewed the existing data and concluded that neither test provides enough useful information beyond other ways of making a decision whether a biopsy should be done. As a result, they have decided against approving these tests. Part of the problem is that a percentage of the cancers detected if the tests are used have a very low risk of causing mortality and therefore finding and treating them may not offer much advantage. A question worth asking is why there is a difference in approval between the US and British regulatory authorities. The full report may help provide more insight.

The Bottom Line: For now, patients with one negative biopsy who are considering either of these two tests should learn more about why they were not approved in Great Britain before deciding what to do.

a2p1c2 Active surveillance is again gaining attention following the publication of another update to the Canadian series of nearly 1,000 patients. For the men with low-risk disease the risk of dying from prostate cancer is only 1.5%. About 20% have now been followed for more than ten years. Using their approach, only about 27% have been treated for their cancer, meaning that nearly three-fourths of the men have not yet been treated. Men were about 10 times more likely to die of some other cause rather than prostate cancer. In the absence of a randomized trial, definitive proof of the relative value of this approach will be lacking. Nevertheless, the cancer mortality is not significantly higher than has been reported in series of low-risk men treated definitively. The PIVOT trial showed only a 2.9% non-significant difference in mortality for men treated conservatively compared to those undergoing surgery and one might expect that had active surveillance rather than watchful waiting been used, the difference probably would be lower.

The Bottom Line: Active surveillance continues to show a low risk of prostate cancer mortality beyond 10 years. Clearly, these results need to be presented to all newly diagnosed men with low–risk disease so they understand the outcomes with this approach and can decide if aggressive therapy is in their best interest.

a3p1c3 To exercise or not to exercise – that is the question for prostate cancer patient. A study by Bonn and co-workers addressed this question in a large cohort of men diagnosed between 1997 and 2002. Men were questioned about their level of exercise based on walking or cycling. Exercising more than one hour per week resulted in a reduced risk of dying from prostate cancer and other causes. There is no doubt that exercise has important health benefits. Unfortunately, this study has several problems. First, it was not a randomized assessment of exercise vs. no exercise. Second, at least from the abstract, no information is provided about the pathology, staging, or treatment to know if the groups were balanced. Third, it is also unclear how authors selected the duration of exercise. Often studies, such as this one, will try out different amounts to run the analysis and then report the one showing a statistical difference. Finally, there is a potential for error when men are asked to report their level and time of each activity.

The Bottom Line: Although exercise has clear general health benefits, this study does not reliably assess its value in men with prostate cancer.

a4p2c2 Estrogen therapy for prostate cancer has been used for nearly 70 years as an alternative to bilateral orchiectomy. Unfortunately, the standard dose (5 mg/day) resulted in a significant increase in the risk for cardiovascular mortality. The eventual development of LHRH agonists plus the cardiovascular risk led to a great drop in the use of this treatment. However, over the years, studies have reported the effect of using lower doses of DES, either 1 mg or 3 mg per day. Some men appear to get an objective response when it is used as second or third line therapy. The study by Tero et al shows a similar result. Unfortunately, the study does not provide information about its impact on survival and since it was a retrospective study, no valid conclusions are possible. Also, neither the value of a PSA response or the time to progression are reliable substitutes for survival.

The Bottom Line: Estrogen appears to have activity as a second or third line agent in men with advanced prostate cancer and is probably worth assessing in a well-done randomized study to determine if it can improve survival.

a5p2c3 A question never adequately assessed is whether radiation to lymph nodes invaded by prostate cancer will benefit patients. In a small, uncontrolled study, Detti et al observed that 24/30 (80%) men had a PSA response to CyberKnife radiation. Unfortunately, a PSA response has an unclear impact on survival. I find studies like this troubling for the following reasons. Are the authors charging patients to receive this therapy? If so, shouldn't patients question why that is appropriate? The information the authors are accumulating will never be able to determine if men are deriving any benefit. Unless they conduct a proper study, no one will know if the therapy is worthwhile.

The Bottom Line: This study using CyberKnife radiation for treating lymph nodes shows a PSA response but regardless of the duration of followup, the value of this therapy will never be known unless a properly controlled study is conducted.

a7p4c1 Is the final scar resulting from a radical prostatectomy important to men? A partial assessment of this question was conducted in a prospective but non-

(Continued on page 8)

THE BOTTOM LINE

(Continued from page 7)

randomized study. They asked patients to complete two questionnaires that assess the scar and found that men undergoing a mini–laparoscopic operation had a better cosmetic outcome compared to the retropubic or standard laparoscopic approach. One of the questionnaires measures surface area of the scar, pigmentation, surface roughness, vascularization, and pliability. Unfortunately, the authors did not do a quality of life assessment to determine if this difference really mattered. Many factors may go in to selecting the method of radical prostatectomy but it seems unlikely that small differences in the scar will trump more important side effects and quality of life issues.

The Bottom Line: A mini–laparoscopic radical prostatectomy may have a better cosmetic result than either the regular laparoscopic or retropubic approach but a randomized study is needed to confirm this finding. More importantly, the question needing an answer is whether this really matters to patients.

MORE EVIDENCE OF HARM FROM SELENIUM *(Continued from page 6)*

nium supplements compared with placebo," Dr. Brasky noted. On the other hand, the same trial showed that men who had high baseline levels of selenium and who were also given selenium supplements were significantly harmed by supplementation.

As reported by *Medscape Medical News*, the risk for high-grade cancer was increased by 91% in men in SELECT with high baseline selenium levels who took 200 µg a day of selenium supplements. "I think the current study really highlights concern that too much of this substance can be a bad thing," Dr. Brasky said.

On average, men in the United States consume 134 µg of selenium per day.

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EFAVIRENZ IN METASTATIC CRPC *(Continued from page 5)*

EFZ was achieved, PSA progression was observed in only 28.6% vs. 81.8% of patients with suboptimal plasma concentrations of EFZ.

Conclusion: Although 600 mg EFZ did not statistically improve the PSA nonprogression rate, our exploratory analysis suggests that higher plasma concentrations of this drug (i.e., use of increased dosages) may be of potential benefit for the treatment of mCRPC.

MECHANISMS OF PROSTVAC IMMUNOTHERAPY *(Continued from page 6)*

vealed that both T cell subsets contributed to anti-tumor efficacy. Characterization of TILs demonstrated that PROSTVAC immunotherapy greatly increased the intra–tumoral ratio of activated effector to regulatory T cells.

Conclusions: PROSTVAC immunotherapy activates broad, highly functional T cell immunity to the PSA target and to endogenous tumor antigens via immune–mediated antigen spreading. These preclinical results further elucidate the mode of action of PROSTVAC immunotherapy and its potential causal relationship to extended overall survival as observed in the PROSTVAC Phase 2 study. The clinical validation is ongoing in the PROSPECT Phase 3 clinical study.

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