Us TOO® PROSTATE CANCER EDUCATION & SUPPORT

HOTSHEET

APRIL 2015

ADD RADIATION TO ANDROGEN DEPRIVATION FOR LOCALLY ADVANCED PROSTATE CANCER

Radiotherapy (RT) added to androgen deprivation therapy (ADT) improves survival with locally advanced prostate cancer, according to eight years' worth of data from a clinical trial. The study is the largest reported trial comparing ADT alone to ADT+RT for locally advanced prostate cancer.

The final results, reported online 17 February 2015 in the *Journal of Clinical Oncology*, are in keeping with an interim analysis published in 2011 that showed a significant overall survival (OS) improvement with the combination. The trial included 603 men randomly assigned to ADT+RT and 602 on ADT alone. The median survival was eight years (range, 0 to 15.2 years).

The addition of RT to ADT was associated with a 30% reduction in the risk of death ($p < 0.001$). The median OS was 9.7 vs. 10.9 years in the ADT-only arm compared with in the ADT+RT arm. The 10-year OS rate was significantly higher in the ADT+RT group (55%) than in the ADT-only group (49%).

The difference in overall survival between the groups resulted from the significant reduction in the risk of death from prostate cancer, as there was no evidence of any differences in deaths from other causes. The treatment groups

(Continued on page 5)

DID PSA TEST'S DECLINE SPUR RISE IN PROSTATE CANCERS?

U.S. recommendations against the PSA test for prostate cancer might have prompted a small but measurable increase in the number of higher-risk cases diagnosed recently, according to a new study. The U.S. Preventive Services Task Force (USPSTF) in 2009 recommended that the PSA test not be used to screen men 75 years or older for prostate cancer, and in 2012 recommended that the PSA not be used for prostate cancer screening at all for any age group.

"The new study relied on data from roughly 87,500 men treated for prostate cancer between 2005 and 2013. In addition to finding an increase of three percent a year for men diagnosed with a PSA of 10 or higher, the researchers discovered nearly double the increase – about six percent per year – for men 75 or older," Schultheiss said. Prior to 2011, there had been a steady decline in the percentage of men with prostate cancer with a PSA of 10 or higher.

PSA levels of 10 or more signify intermediate or high-risk prostate cancer. "This trend suggests that an additional 14,000 men were diagnosed with higher-risk prostate cancer in 2014, and that an estimated 1,400 would have died from the disease that year," said study co-author Timothy Schultheiss, director of radiation physics at City of Hope Medical Center in Duarte, CA.

(Continued on page 5)

GENOMIC CLASSIFIER SCORE IDENTIFIES RISK OF METASTASIS AND BENEFIT OF ADJUVANT RADIOTHERAPY AFTER RADICAL PROSTATECTOMY

In a study reported online in the *Journal of Clinical Oncology*, Den et al found that a 22-biomarker genomic classifier score was predictive of a greater risk of metastasis and benefit of adjuvant vs. salvage radiotherapy (RT) after radical prostatectomy (RP) for prostate cancer.

The study involved genetic classifier scores (GenomeDx PCa genomic database) from 188 men with pT3 or margin-positive prostate cancer who received RT after RP at Thomas Jefferson University and Mayo Clinic between 1990 and 2009.

The cumulative incidence of metastasis at 5 years after RT was 0%, 9%, and 29% for low, average, and high genomic classifier scores ($P=0.002$). By comparison, 5-year cumulative incidence rates in men with low, average, and high Cancer of the Prostate Risk Assessment Postsurgical scores (CAPRA-S) were 13%, 2%, and 14% ($P=0.04$). On multivariate analysis including the two approaches, hazard ratios (HRs) were 1.69 ($P<0.001$) per 0.10-unit increase in genomic classifier score and 1.28 ($P=0.0282$) per 1-unit increase in CAPRA-S.

On univariate analysis, genomic classifi-

(Continued on page 4)

THIS ISSUE OF THE US TOO PROSTATE CANCER HOTSHEET IS MADE POSSIBLE BY CHARITABLE CONTRIBUTIONS FROM

150 Years Science For A Better Life

astellas Leading Light for Life

MEDIVATION Driven by science. Focused on life.

Takeda MILLENNIUM THE TAKEDA ONCOLOGY COMPANY

PINTS for PROSTATES

TEVA Oncology

abbvie BAVARIAN NORDIC

AND PEOPLE LIKE YOU!

2720 S. RIVER RD., STE. 112, DES PLAINES, IL 60018
PHONE: (630) 795-1002 / FAX: (630) 795-1602

WEBSITE: WWW.USTOO.ORG

THE CLINICAL SIGNIFICANCE OF PERSISTENT CANCER CELLS ON PROSTATE BIOPSY AFTER HIGH DOSE-RATE BRACHYTHERAPY BOOST FOR INTERMEDIATE-RISK PROSTATE CANCER

D'Alimonte L, Helou J, Sherman C, et al

Brachytherapy 25 November 2014

Purpose: To evaluate the association between post-treatment biopsy results and the probability of biochemical disease-free survival (bDFS).

Methods and Materials: Two sequential prospective clinical trials were undertaken in men with intermediate-risk prostate cancer (T1-T2 with either Gleason score 7 and PSA level lower than 20 ng/mL or Gleason score 6 and PSA level of 10-20 ng/mL). All men had high dose-rate brachytherapy (two fractions of 10Gy separated by one week or a single 15-Gy fraction) followed by external beam radiotherapy (EBRT). Both study groups were followed prospectively with regular PSA readings and prostate biopsy at two years. Biopsies were reported as: positive = malignant cells with no or only partial RT effect, negative = no malignant cells seen and indeterminate = malignant cells with marked RT effect. Biochemical failure was defined using the nadir +2ng/mL definition and estimated using the Kaplan-Meier curves. Fisher exact test was performed to investigate any relationships between high dose-rate treatment and biopsy results.

Results: A total of 181 men were included in this analysis. The median follow-up for all men was 6.2 years (range, 0.3-10.5). Post-treatment biopsy was performed in 111 men of which 82 (74%) were negative, 17 (15%) indeterminate, and 12 (11%) malignant. The five-year bDFS was 97.5%, 93.8%, and 83.3% for those with benign, indeterminate, and malignant biopsies, respectively (p = 0.4398). Median PSA nadir was 0.08 ng/mL (range, 0.01-3.63), with no difference in PSA change over time by treatment (p = 1.0) or biopsy result (p = 0.44).

Conclusions: Routine biopsy at two years was not able to reliably predict which patients would ultimately fail as even those with a positive biopsy had a long-term bDFS higher than 80%.

RADIOGRAPHIC PROGRESSION-FREE SURVIVAL AS A RESPONSE BIOMARKER IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER: COU-AA-302 RESULTS

Morris MJ, Molina A, Small EJ, et al

J Clin Oncol 26 January 2015 Epub

Purpose: Progression-free survival (PFS) in metastatic castration-resistant prostate cancer (mCRPC) trials has been inconsistently defined and poorly associated with overall survival (OS). A reproducible quantitative definition of radiographic PFS (rPFS) was tested for association with a coprimary end point of OS in a randomized trial of abiraterone in patients with mCRPC.

Patients and Methods: rPFS was defined as ≥ two new lesions on an eight-week bone scan plus two additional lesions on a confirmatory scan, ≥ two new confirmed lesions on any scan ≥ 12 weeks after random assignment, and/or progression in nodes or viscera on cross-sectional imaging, or death. rPFS was assessed by independent review at 15% of deaths and by investigator review at 15% and 40% of deaths. rPFS and OS association was evaluated by Spearman's correlation.

Results: A total of 1,088 patients were randomly assigned to abiraterone plus prednisone or prednisone alone. At first interim analysis, the hazard ratio (HR) by independent review was 0.43 (95% CI, 0.35 to 0.52; P <0.001; abiraterone plus prednisone: median rPFS, not estimable; prednisone: median rPFS, 8.3 months). Similar HRs were obtained by investigator review at the first two interim analyses (HR, 0.49; 95% CI, 0.41 to 0.60; P <0.001 and HR, 0.53; 95% CI, 0.45 to 0.62; P <0.001, respectively), validating the imaging data assay used. Spearman's correlation coefficient between rPFS and OS was 0.72.

Conclusion: rPFS was highly consistent and highly associated with OS, providing initial prospective evidence on further developing rPFS as an intermediate end point in mCRPC trials.

DOC MOYAD'S WHAT WORKS & WHAT IS WORTHLESS COLUMN, ALSO KNOWN AS "NO BOGUS SCIENCE" COLUMN – "Metformin, cancer, and why you should just appreciate that the glass even exists?"

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

Editor's Note: Us TOO invites 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 are not necessarily those of Us TOO International.

Bottom Line: Metformin given to non-diabetic breast cancer patients with a BMI of just 27 (overweight and not obese on average) compared to placebo significantly reduced weight (-3%), glucose (-3.8%), insulin (-11.1)%), and hs-CRP (-6.7%) within 6 months. This suggests that it should also be considered in some prostate cancer patients in order to just make them more heart healthy (aka lose weight and prevent type 2 diabetes).

As you may or may not know **I love metformin** (not a romantic love but a medical love of course – there is a slight difference)!!! Why? It is for several reasons including the fact that it is dirt cheap (like me), generic – been around decades (like me), comes from a "natural source" (French Lilac) and has already proven to reduce the risk of type 2 diabetes and is arguably the greatest and safest weight loss drug ever invented (all for just pennies a day). It is also being studied in over 100 clinical trials in cancer and many of these studies are in prostate cancer. However, breast cancer already has a phase III trial with metformin and women that are **non-diabetic**.[1]

This is such a "groovy" study (in deference to those who grew up in the 1970s) and while we wait on final results many have argued whether or not metformin fights cancer??? This is a silly argument because for pennies a day we already have a good idea that it can make some cancer patients healthier or more heart-healthy by reducing their weight and blood sugar and some key inflammatory markers. And, this is what this preliminary six-month study from the phase III trial showed, which is fabulous. Another study I reviewed a while ago also showed these benefits can happen for men on LHRH treatment for prostate cancer,[2] and new preliminary evidence suggests it may also slow the progression of CRPC (castrate-resistant prostate cancer).[3] The dosage used in this current study was 850 mg once a day for four weeks and then another 850 mg was added (total dosage was 1,700 mg). The problem I have is that many folks argue back and forth (blah blah blah) as to whether or not metformin will reduce the risk of cancer or cancer recurrence and that should NOT be the initial argument. The fact that it could reduce the risk of the number-one cause of death over the last 115 years (cardiovascular disease) in men and women with cancer and for just pennies a day makes it a good candidate to use in some patients now. And, if it also lowers the risk of cancer recurrence then that would be a nice bonus, of course. There are some moments where the glass is not just about being half-full or half-empty but simply appreciating that the glass even exists! And in the case of metformin, this is one glass that I am happy still exists!

References:

1. Goodwin PJ, Parulekar WR, Gelmon KA, et al. Effect of metformin vs placebo on metabolic factors in NCIC CTG MA.32. J Natl Cancer Inst 2015, 4 March 2015; Epub.
2. Nobes JP, Langley SE, Klopper T,et al. A prospective, randomized pilot study evaluating the effects of metformin and lifestyle intervention on patients with prostate cancer receiving androgen deprivation therapy. BJU Int 2012; 109: 1495-1502.
3. Rothermundt C, Hayoz S, Templeton AJ, et al. Metformin in chemotherapy -naïve castration-resistant prostate cancer: A multicenter phase 2 trial (SAKK 08/09). Eur Urol 2014; 66: 468-474.

PROSTATE CANCER SURGERY MAY IMPAIR SEX FOR BOTH PARTNERS

Both members of a couple can experience diminished sexual function after a man has prostate cancer surgery, Swiss researchers find, suggesting that treatment should include sex counseling for men and their partners. The researchers studied sexual function and satisfaction after men had a type of cancer surgery designed to remove the entire prostate, including semen glands, but protect nearby nerves that are involved in erections.

"Typically, even with nerve sparing, a man may have difficulties for months before he gets back to a more normal erectile function, and then he will have an orgasm that doesn't include ejaculation," said Dr. Vincent Laudone, a urologic surgeon at Memorial Sloan Kettering Cancer Center in New York who wasn't involved in the study. "Any treatment that doesn't involve an up-front, detailed discussion with both members of a couple is lacking," Dr. Laudone said.

Dr. Christophe Iselin, with the division of urologic surgery at Geneva University Hospital in Switzerland, and colleagues write in the January 2015 issue of *International Journal of Impotence Research* that screening is leading to more men, and younger men being treated for prostate cancer.

To assess the effect this may be having on couples' sexual health, they analyzed data on 21 couples who completed questionnaires about sex before the men had prostate cancer surgery and again six months after the procedure. The average age of the study participants was 62.4 for men and 60.7 for women. Bilateral nerve sparing, the most effective at preserving erectile function, was done in 12 procedures. The remaining nine operations involved nerve sparing on just one side.

As typically happens with prostate surgery, the men reported decreased erectile function after the fact, with a steeper decline after unilateral nerve sparing. But the women also reported decreased sexual function after the men had surgery, with declines in desire, arousal, lubrication, orgasm and satisfaction.

"The stress of cancer treatment and the disruption in the couple's usual pattern of intimacy can leave both partners feel-

(Continued on page 6)

GENOMIC CLASSIFIER

(Continued from page 1)

er score, preoperative PSA level, and radiotherapy modality were significant predictors of metastasis. On multivariate analysis not including CAPRA-S, genomic classifier score and presurgery PSA level (HR=2.12, *P*=0.0022) were independent predictors of metastasis. Genomic classifier score was associated with HRs for metastasis of 1.90 for every 0.10-unit increase (*P* <0.001) and 9.58 (*P*=0.013) for high vs. low score.

Within the low genomic classifier score group (score <0.4), there was no difference in cumulative incidence of metastasis with adjuvant vs. salvage radiotherapy (*P*=0.79). However, for men with higher scores (≥0.4), the cumulative incidence at five years was 6% vs. 23% (*P* <0.01) for adjuvant vs. salvage RT.

The investigators concluded: "In patients treated with post-[radical prostatectomy radiotherapy], [genomic classifier score] is prognostic for the development of clinical metastasis beyond routine clinical and pathologic features. Although preliminary, patients with low [genomic classifier] scores are best treated with salvage [radiotherapy], whereas those with high [genomic classifier] scores benefit from adjuvant therapy. These findings provide the first rational selection of timing for post-[radical prostatectomy radiotherapy]."

Robert B. Den, MD, of Sidney Kimmel Medical College at Thomas Jefferson University, is the corresponding author of the *Journal of Clinical Oncology* article. Dr. Den and Kasra Yousefi, MSc, of GenomeDx Biosciences, Vancouver, contributed equally to the article.

The content in this post has not been reviewed by the American Society of Clinical Oncology, Inc. (ASCO®) and does not necessarily reflect the ideas and opinions of ASCO®.

The ASCO Post, 18 February 2015

NON-STEROIDAL ANTIANDROGEN MONOTHERAPY COMPARED WITH LUTEINISING HORMONE-RELEASING HORMONE AGONISTS OR SURGICAL CASTRATION MONOTHERAPY FOR ADVANCED PROSTATE CANCER: A COCHRANE SYSTEMATIC REVIEW

Kunath F, Grobe HR, Rücker G, et al

BJU Int 18 December 2014; Epub ahead of print

Objective: To assess the effects of non-steroidal antiandrogen (AA) monotherapy compared with luteinising hormone-releasing hormone agonists (LHRH-A) or surgical castration monotherapy for treating advanced hormone-sensitive stages of prostate cancer.

Materials and Methods: We searched the Cochrane Prostatic Diseases and Urologic Cancers Group Specialized Register (PROSTATE), the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Web of Science with Conference Proceedings, three trial registries and abstracts from three major conferences to 23 December 2013, together with reference lists, and contacted selected experts in the field and manufacturers. We included randomised controlled trials comparing non-steroidal AA monotherapy with medical or surgical castration monotherapy for men in advanced hormone-sensitive stages of prostate cancer. Two review authors independently examined full-text reports, identified relevant studies, assessed the eligibility of studies for inclusion, extracted data and assessed risk of bias as well as quality of evidence according to GRADE. We used Review Manager 5.2 for data synthesis and used the fixed-effect model as primary analysis (when heterogeneity low with I2 less than 50%); we used a random-effects model when confronted with substantial or considerable heterogeneity (I2 ≥50%).

Results: Eleven studies involving 3,060 randomly assigned participants were included in this review. Use of non-steroidal AAs decreased overall survival (OS, hazard ratio (HR) 1.24, 95% confidence interval (CI) 1.05 to 1.48, six studies, 2,712 participants) and increased clinical progression (one year: risk ratio (RR) 1.25, 95% CI 1.08 to 1.45, five studies, 2,067 participants; 70 weeks: RR 1.26, 95% CI 1.08 to 1.45, six studies, 2,373 participants; two years: RR 1.14, 95% CI 1.04 to 1.25, three studies, 1,336 participants), as well as treatment failure (one year: RR 1.19, 95% CI 1.02 to 1.38, four studies, 1,539 participants; 70 weeks: RR 1.27, 95% CI 1.05 to 1.52, five studies, 1,845 participants; two years: RR 1.14, 95% CI 1.05 to 1.24, two studies, 808 participants), compared with medical or surgical castration. The quality of evidence for OS, clinical progression and treatment failure was rated as moderate according to GRADE. Use of non-steroidal AAs increased the risk for treatment discontinuation due to adverse events (RR 1.82, 95% CI 1.13 to 2.94, eight studies, 1,559 participants), including events such as breast pain (RR 22.97, 95% CI 14.79 to 35.67, eight studies, 2,670 participants) and gynaecomastia (RR 8.43, 95% CI 3.19 to 22.28, nine studies, 2,774 participants) The risk of other adverse events, such as hot flashes (RR 0.23, 95% CI 0.19 to 0.27, nine studies, 2,774 participants) was decreased when non-steroidal AAs were used. The quality of evidence for breast pain, gynaecomastia and hot flashes was rated as moderate according to GRADE. The effects of non-steroidal AAs on cancer-specific survival and biochemical progression remained unclear.

Conclusions: Non-steroidal AA monotherapy compared to medical or surgical castration monotherapy for advanced prostate cancer is less effective in terms of OS, clinical progression, treatment failure and treatment discontinuation due to adverse events. Evidence quality was rated as moderate according to GRADE; therefore further research is likely to have an important impact on results for patients with advanced but non-metastatic prostate cancer treated with non-steroidal AA monotherapy.

ADD AD+RT FOR LOCALLY ADVANCED PROSTATE CANCER

(Continued from page 1)

did not differ in the rates of impotence/ libido, hot flushes, urinary frequency, ischemia, hypertension, or cardiovascular toxicities. Only two of 589 assessable patients in the ADT + RT group experienced bowel adverse events greater than grade 3.

"Although there are undoubtedly patients for whom RT or indeed any curative therapy would be inappropriate because of age, comorbidity, or other factors, we conclude that patients with clinically node-negative, locally advanced prostate cancer who are suitable for additional RT should be offered that option, an opinion shared by European and North American guidelines," Dr. Malcolm D. Mason from Cardiff University School of Medicine, UK, and colleagues write.

Dr. Juanita Crook, professor of radiation oncology at the University of British Columbia in Kelowna, Canada, told Reuters Health by email, "The improvement in overall survival with the addition of external radiotherapy mirrors the reduction in deaths from prostate cancer. It is quite remarkable that the addition of a local treatment is actually able to improve overall survival in 70-year-old men when there are so many other competing causes of mortality."

She agreed with the authors that "it is inappropriate to just put a patient on androgen deprivation because his chances of cure are perceived as low (locally advanced disease, high PSA, high Gleason). The addition of EBRT (external beam RT) may not cure, but it will improve overall survival, at minimal cost in terms of quality of life."

Dr. Michael Abern from the University of Illinois at Chicago, who also was not involved in the new work, said "the main limitation of treating locally advanced or high risk prostate cancer with ADT or ADT + RT is the uncertainty of clinical staging. Our data has shown that many prostate cancers thought to be locally advanced based on PSA or rectal exam, and even imaging studies, are downstaged when the prostate is removed surgically. Furthermore, lymph node staging with available imaging studies is inaccurate with regard to the gold standard of surgical lymphadenectomy."

"While this article supports the concept of treatment of the local tumor in locally advanced prostate cancer, a more optimal approach may be to include surgery, RT, and ADT for maximal chance of cure," he told Reuters Health by email. "Sequencing surgery first allows accurate staging which can help to appropriately select men for RT and ADT as needed."

Dr. Quoc-Dien Trinh from Harvard Medical School and Dana-Farber/ Harvard Cancer Center, Boston, also stressed the importance of other treatment options. "The authors claim that given the level 1 evidence presented here and by others, alternatives to ADT + RT should only be administered in the context of a randomized controlled trial. I strongly disagree with this statement," he said in an email to Reuters Health.

"First, their study was designed to assess RT vs. RT + ADT, and should be interpreted within that framework," Dr. Trinh explained. "It did not look at RT + ADT vs. watchful waiting, RT + ADT vs. surgery, RT + ADT vs. surgery + RT + ADT, etc. Second, there is quality evidence to suggest that surgery is an excellent first-line treatment approach for locally advanced disease, and there is level 1 data to support the use of adjuvant radiation therapy AFTER surgery in the presence of adverse features. Major guidelines, and most clinicians, would agree with this statement. For example, the National Comprehensive Cancer Network Guidelines for prostate cancer clearly state that both RT + ADT and upfront radical prostatectomy are acceptable treatment options for high-risk prostate cancer."

Dr. Trinh concluded, "Patients should be reminded of the dangers of ADT, including increased risk of cardiovascular disease and bone fractures. The decision to initiate ADT should not be taken lightly, especially when harms may outweigh the benefits."

Reuters Health, 24 February 2015

MORE HIGH-RISK CANCERS

(Continued from page 1)

"We believe our data indicate that the USPSTF might reconsider their recommendation," Schultheiss said. "We need to be intelligent about who we screen and who we treat. We're not suggesting that everyone be screened using PSA, but we're not suggesting that no one be screened using PSA. The USPSTF's position of recommending against all PSA screening is 'extreme'," he added.

In response, USPSTF Chairman Dr. Michael LeFevre said the study authors' conclusions regarding the PSA test were premature and based on incomplete data. He said, "It is unclear, from the data made available to us at this time, how this study could be used to draw conclusions about the impact of the USPSTF's 2012 recommendation on PSA screening for prostate cancer on the number of high-risk cancers being diagnosed either before or after the recommendation."

Schultheiss said he and his colleagues did examine the severity of prostate cancer in the men studied, and those indicators "did not change appreciably during the same period of time." Findings from the study were presented at the American Society of Clinical Oncology annual meeting in Orlando, FL.

Other studies call into question the effectiveness of PSA screening. One reason is that many men with prostate cancer do not die from their cancer. On the other hand, surgery or radiation therapy to treat prostate cancer can lead to a number of side effects, such as impotence and incontinence. This raises the question of whether treatment is worthwhile given that it can significantly harm a man's quality of life.

"If you don't screen people, then when they show up with prostate cancer, the horse is out of the barn," Schultheiss said. "By missing early disease, then you're going to catch it when it's later, when it's palpable or symptomatic."

Dr. Charles Ryan, a medical oncologist at UC San Francisco and an ASCO expert, noted "This is a study that really does add some new insight into the ongoing debate over the risks and benefits of prostate cancer screening."

HealthDay, 24 February 2015

SEX FOR BOTH PARTNERS

(Continued from page 3)

ing less interested in sexual activity," said Dr. Andrea Bradford, an assistant professor of gynecologic oncology and reproductive medicine at The University of Texas MD Anderson Cancer Center in Houston, TX.

"Even though women aren't the ones having surgery, the disruption of their regular sex life in the weeks or months immediately after the man's operation can make sex more painful when relations resume," said Dr. Bradford, who wasn't involved in the study.

"The female partners in this study were in mid-life or older, which means most of them were post-menopausal," Dr. Bradford said. "Regular sexual activity can help prevent or slow the normal vaginal changes that occur after menopause, but after a long period of sexual abstinence women may be surprised to find that they have more difficulties than before with lubrication or genital pain."

Limitations of the study include the small sample, taken only from couples who agreed to sexual assessments, and the short six-month follow-up period for a procedure that can inhibit erectile function for as long as two to three years, the researchers point out in their report.

Going beyond the mechanics of sexual function, the study team also looked at how satisfied couples were with their relationships. The couples reported a dip in satisfaction six months after surgery, but the decline wasn't statistically significant.

"While other studies have found that relationships aren't affected in those first months, longer-term studies have shown declines in sexual and emotional intimacy as well as relationship satisfaction," said Dr. Daniela Whittmann, a clinical assistant professor of urology at the University of Michigan in Ann Arbor, who wasn't involved in the study. "Partners are still not sufficiently included in discussions surrounding prostate cancer treatment," she added.

Reuters Health, 17 February 2015

OBSERVATION FOR LOW-RISK PROSTATE CANCER INCREASING PROPORTIONALLY

The proportion of men with low-risk prostate cancer entering observation increased by more than 50% from 2004 to 2009 but remained less than 30%, analysis of a national database showed.

Overall, use of observation increased slightly from 17% to 20% during the five-year period but jumped from 18% to 29% in the subgroup of men with low-risk disease. The odds for observation doubled for men in the 66 to 69 age group, those with low-risk disease, and patients with no comorbidities, Chad Ritch, MD, MBA, of the University of Miami, and colleagues reported online in *The Journal of Urology*.

The rationale for the study came from concern about overtreatment of localized prostate cancer, particularly low-risk disease. Moreover, uncertainty exists about the uptake of observation (surveillance) as a disease management strategy. The authors had a particular interest in temporal trends in the use of observation for men with low-risk disease "who were young and healthy enough to undergo treatment."

Ritch and colleagues retrospectively analyzed of the Medicare-linked Surveillance, Epidemiology, and End Results (SEER) database. They identified all men with newly diagnosed localized prostate cancer from 2004 through 2009.

The primary outcome was observation within one year after diagnosis. Observation was defined as absence of any accepted treatment for localized prostate cancer, including surgery, radiotherapy, cryoablation, and primary androgen deprivation therapy. The authors defined low-risk disease in accordance with the D'Amico classification system.

The search of the SEER database identified 66,499 men with newly diagnosed localized prostate cancer, of whom 34% met criteria for low-risk, 40% intermediate-risk, and 26% high-risk. Subsequently 12,007 (18%) entered observation within a year of diagnosis.

Use of observation increased modestly but significantly ($P<0.001$) in the overall analysis. Analysis by risk classification showed that use of observation in low-risk patients was the driving force behind the overall increase.

When the authors examined predictors of observation, they found that white men, ages 66 to 69, with low-risk disease and no comorbidities were twice as likely to enter observation in 2009 as compared with 2004 (OR 2.12, 95% CI 1.73-2.59).

Age, risk status, comorbidity status, and race had independent associations with observation ($P<0.001$). Men who were older, had low-risk disease, and had a higher number of comorbidities also had significantly higher odds of entering observation as did black men ($P<0.001$).

Despite the increased use of observation documented by the study, the authors acknowledged that "use of observation must expand further to improve the benefit-to-harm ratio of prostate cancer detection."

MedPage Today, 17 February 2015

BAVARIAN NORDIC VACCINE HELPS PROLONG LIFE IN PROSTATE CANCER TRIAL

An experimental therapeutic vaccine from Danish drugmaker Bavarian Nordic helped significantly extend survival in patients with advanced prostate cancer, according to results of a small early-stage trial conducted by the U.S. National Cancer Institute. The vaccine is designed to trigger an immune system response against prostate cancer cells. The study involved 30 patients with metastatic castration-resistant prostate cancer (CRPC).

Patients were treated with the company's Prostvac vaccine, in addition to escalating doses of Bristol-Myers Squibb Co's immunotherapy drug ipilimumab (Yervoy®), an approved treatment for advanced melanoma. On average, patients taking both drugs survived 31.3 months, compared with a predicted survival period of 18.5 months that had been based on historical survival data for older chemotherapy treatments.

(Continued on page 8)

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 are not necessarily those of Us TOO International.

a1p1c1 Over the years, significant progress has been made in the management of men with locally advanced prostate cancer (T3-T4) or high-risk localized disease (Gleason 8-10). Based on randomized studies, men who receive radiation therapy after a radical prostatectomy have a significantly better survival and lower risk of dying from prostate cancer if the radiation is combined with androgen deprivation therapy (ADT). Since those studies only compared radiation with or without ADT, an unanswered question is whether the radiation was really necessary or could ADT be used by itself. The study by Crook and co-workers has partly answered that question. They found a significantly higher survival and lower risk of dying from prostate cancer in the men getting the combination therapy. The risk of dying from prostate cancer was cut by more than 50%. Based on other well-done studies, lifelong ADT does not appear to be necessary. The optimal duration is somewhere between 18-36 months. Administering ADT for only six months, however, is significantly inferior to the longer duration. One problem with these studies is the dose of radiation (65-69 Gy) was lower than commonly used today (74-82 Gy). At this time, no studies have been done to assess the optimal duration of ADT when a higher dose or radiation is used. We also have no idea how this therapy would compare with surgery combined with radiation. Although some of the comments in the *HotSheet* article are very favorable for surgery followed by radiation for this high-risk group, a randomized study is needed to determine if that is as effective as the combination of XRT plus ADT.

The Bottom Line: Men with locally advanced prostate cancer have better survival if they receive external radiation plus ADT rather than either one alone.

a2p1c2 Concerns about the USPTF recommendations against screening are unlikely to stop any time soon. The latest one comes from Schultheiss and co-workers who looked at the incidence of men being diagnosed with a PSA greater than 10 ng/mL between 2005 and 2013. They found about a 3% increase in the frequency between 2011 and 2013 and then they calculated a hypothetical number of men who might be diagnosed with high-grade disease in 2014 or die from their disease by not being tested. Unfortunately, their analysis has several flaws. First, by noting the increase in 2011 and 2012, one cannot conclude that it has anything to do with the task force recommendation, which came out in 2012. Second, it is not valid to calculate expected deaths, only a true follow-up can determine the death rate. Third, they are missing very important data; was there a measurable change in the proportion of men getting a PSA test.

The Bottom Line: The impact of the latest USPTF guidelines regarding screening cannot be reliably assessed by this type of analysis.

a3p1c3 Which is better following radical prostatectomy for pT3 or margin positive disease – adjuvant or salvage radiation? Randomized studies have demonstrated a small survival benefit for adjuvant therapy, but most of the men will receive unnecessary radiation. Finding a way to identify those patients that would benefit from adjuvant therapy is an important research question. A genomic classifier score may provide useful information. Dr. Den and co-workers analyzed patients with this test or the Capra-S score and found that men with a high genomic score (>0.4) had a much lower incidence of metastases if they received adjuvant therapy but those with a lower score did not appear to have different rates. Caution is needed because the study was not randomized, so an unclear selection bias might have contributed to the results. Nevertheless, these data provide support for a prospective, randomized trial in men with a high score to assess the impact on survival.

The Bottom Line: Using a genomic classifier test may be able to help decide which men would benefit from adjuvant radiation after radical prostatectomy.

a4p2c2 What about men with intermediate risk cancer for which randomized studies have shown a survival benefit by also combining external radiation and a shorter course of ADT? D'Alimonte and co-workers reported on 181 men who received high dose rate brachytherapy followed by external radiation. The authors looked at biopsy results and follow-up PSA levels. They found that men with a positive biopsy at two years had a higher rate of biochemical failure at a median of 6.2 years. The authors conclude that even having a positive biopsy still had resulted in only a 20% biochemical failure rate. Although proponents of this treatment are likely to use these results to support this therapy, several problems exist. First, biochemical outcome is not a reliable enough predictor of effectiveness for RT. Second, only 111 out of 181 men had a biopsy, which could underestimate the true failure rate. Lastly, and most importantly, there will be no way to determine the relative merits of this therapy compared to external radiation plus ADT or to surgery. Sadly, this is yet one more example of men undergoing treatment without knowing if they are getting the best outcome.

The Bottom Line: Is high dose-rate brachytherapy plus EBRT a good therapy for intermediate risk prostate cancer? Sadly, that question will remain unanswered until a well-done study is done.

a7p4c2 Ever since anti-androgens became available, many doctors have questioned whether they could be used instead of medical or surgical castration for men with advanced disease. Two studies were done using bicalutamide (Casodex) in men with locally advanced, non-metastatic disease with mixed results. As a result, the FDA decided to not approve an anti-androgen for this indication because a clear benefit was not established. In this HotSheet, Kunath and co-workers conducted a literature review for randomized

(Continued on page 8)

BAVARIAN NORDIC VACCINE

(Continued from page 6)

Among the 15 patients who received the highest 10 milligram dose of Yervoy in combination with Prostvac, 20% remained alive at 80 months.

Data from the combination trial were especially impressive, considering that Yervoy had previously failed in Bristol-Myers' own trials to prolong survival in patients with advanced prostate cancer.

Complete data from the Prostvac study were presented at the 2015 Annual Genitourinary Cancers Symposium in Orlando, FL.

Reuters, 25 February 2015

THE BOTTOM LINE *(Continued from page 7)*

studies comparing the different therapies. They found that the anti-androgen was inferior to the LHRH agonist in terms of overall survival and disease of progression. Finding out the difference in survival at five years would be worth doing because some men might still want an anti-androgen due to a more favorable side effect profile compared to an LHRH agonist.

The Bottom Line: Anti-androgens are inferior to medical castration for men with advanced prostate cancer.

a9p6c2 Are too many men receiving unnecessary local therapy for their newly diagnosed prostate cancer? Monitoring the number of men placed on active surveillance is one way to answer that question. Ritch and colleagues used the SEER database to assess the use of active surveillance between 2004 and 2009. Although they found a significant increase in AS for men with low-risk disease, from 18% to 29%, several questions remain. First, we do not know exactly why AS was chosen. Did the doctor make a recommendation or have men become more knowledgeable about the relative value of this therapy and then chose it? Second, what are the reasons why more men are not being placed on this treatment? Three possibilities are: doctors may have a treatment bias, or, men and their significant others are not being given accurate and complete information about AS, or, patients may be unwilling to accept a small risk of progression and would prefer to err on the side of overtreatment. Regardless of the answers, more work is needed to help men avoid unnecessary treatment.

The Bottom Line: The use of AS is increasing, but still too many men may be receiving unnecessary treatment.

HOTSHEET PERSONAL SUBSCRIPTIONS AVAILABLE

We can deliver the *HotSheet* newsletter right to your home or office. Support the creation and distribution of the *HotSheet* with a suggested annual subscription donation of $35 for 12 issues (includes shipping and handling). To obtain an order form or to order online, go to: www.ustoo.org/Hot_Sheets.asp, or call 1-800-808-7866 (1-800-80-UsTOO).

US TOO INTERNATIONAL:

Our Mission

Be the leading prostate cancer organization helping men and their families make informed decisions about prostate cancer detection, treatment and side effects through support, education and advocacy.

SEA BLUE® SUPPORT • EDUCATE • ADVOCATE

US TOO INTERNATIONAL

PROSTATE CANCER EDUCATION & SUPPORT NETWORK

SEA Blue

SUPPORT • EDUCATE • ADVOCATE

US TOO INTERNATIONAL TAX DEDUCTIBLE DONATION

Name: _____ Company: _____

Address: _____ Suite/Unit #:_____

City: _____ State: _____ ZIP: _____ Country: _____

Phone: ( ) _____ Fax: ( ) _____ Email: _____

Please accept my enclosed tax-deductible donation to Us TOO International, a non-profit 501(c)(3) organization.

Amount: _____ $50 _____ $75 _____ $100 _____ $200 Other: $ _____ Check # _____

VISA/MC/AMEX/DISC # _____ Expiration Date: _____ /_____ CVV#: _____

Signature _____ Date: _____

☐ Check here if you wish to remain anonymous Annual Report donor recognition listing

US TOO INTERNATIONAL, 2720 S. River Road, Suite 112, Des Plaines, IL 60018