Us TOO® PROSTATE CANCER EDUCATION & SUPPORT

HOTSHEET

July 2014

Delaying ADT Does No Harm in Prostate Cancer

Men with PSA relapse after treatment for prostate cancer lived just as long whether androgen deprivation therapy (ADT) was delayed or begun immediately, a large observational study showed. When ADT was delayed until symptoms appeared, patients had a median 5-year survival of 87.2%, versus 85.1% for men who started treatment immediately after biochemical relapse (BCR). The two groups had an identical 10-year survival of 71.6%.

Prostate cancer-specific mortality (PCSM) also did not differ at 5 or 10 years according to the timing of ADT, reported Xabier Garcia-Albeniz, MD, of Harvard University. "Our analysis suggests that men undergoing immediate ADT initiation at PSA-only relapse had similar survival to those who deferred ADT initiation at progression or two or more years after PSA relapse in the absence of clinical progression," Garcia-Albeniz said during a press briefing that preceded the 2014 American Society of Clinical Oncology (ASCO) meeting.

Noting the observational nature of the study, he added that the results provide only a preliminary answer to the question of whether deferred ADT after BCR harms patients with respect to survival, and that the answer is based on the assumption that no unmeasured confounding factors were overlooked. An ongoing phase III trial comparing the two strategies will provide a definitive answer.

(Continued on page 5)

Adding Chemotherapy to Hormone Therapy in Men with Newly Diagnosed Metastatic Prostate Cancer Leads to 'Unprecedented Improvement' in Median Survival

Starting chemotherapy along with hormone therapy in men with newly diagnosed hormone-sensitive prostate cancer improved overall survival (OS) by more than 13 months compared with treatment with hormone therapy alone, a phase III study found (Abstract LBA2). The survival benefit was even greater in men with high-volume disease, at 17 months.

"This is one of the biggest improvements in survival we have seen in a trial involving patients with an adult metastatic solid tumor," said Christopher Sweeney, MBBS, of the Dana-Farber Cancer Institute, at a press briefing. "The certainty of the data is strong for patients with a high volume of metastatic disease and clearly justifies the treatment burden."

Dr. Sweeney presented the results of the E3805 trial comparing "upfront" chemotherapy plus androgen deprivation therapy (ADT) with treatment with ADT alone in men with metastatic prostate cancer. The trial enrolled 790 men between July 2006 and November 2012, who were randomly assigned to ADT plus six cycles of docetaxel or ADT alone. At enrollment, patients were stratified by extent of metastatic disease as high-volume or low-volume. Chemo-

(Continued on page 4)

Study Reveals More than One-Third of Patients with 'Low-Risk' Prostate Cancer on Standard Biopsy Have More Aggressive Tumors on Targeted Biopsy

According to a new study by researchers at the University of California, Los Angeles, selection of men for active surveillance (AS) for prostate cancer should be based not on conventional biopsy, but on a new, imaging-guided targeted prostate biopsy. The new method is now a routine part of the UCLA AS program. The study findings were published in *The Journal of Urology*.

Researchers found that conventional "blind" biopsy failed to reveal the true extent of presumed low-risk prostate cancers, and that when targeted biopsy was used, more than one-third of these men had more aggressive cancers than they thought. Aggressive cancers were not detected by conventional blind biopsy using ultrasound alone, and the men were referred to UCLA's AS program thinking they were at no immediate risk.

The targeted biopsy method is performed by combining magnetic resonance imaging (MRI) with real-time ultrasound in a device known as the Artemis. Previous work from UCLA demonstrated the value of the new procedure in finding cancers in men with rising PSA who had negative conventional biopsies. This study is the first to show the value of using it early in the selection process for men interested in AS.

(Continued on page 5)

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EARLY RETURN OF CONTINENCE IN PATIENTS UNDERGOING ROBOT -ASSISTED LAPAROSCOPIC PROSTATECTOMY USING MODIFIED MAXIMAL URETHRAL LENGTH PRESERVATION TECHNIQUE

Hamada A, Razdan S, Etafy MH, et al

J Endourol 16 April 2014; Epub

Purpose: To evaluate the impact of maximal urethral length preservation (MULP) technique in comparison with posterior urethral reconstruction and anterior bladder suspension (PRAS) technique on the continence rates (CR), time to achieve continence among patients with prostate cancer (PCa) undergoing robot-assisted laparoscopic prostatectomy (RALP).

Patients and Methods: We prospectively analyzed the CR, time to achieve continence, pre- and postoperative prostate-specific antigen (PSA) levels, rates of positive margins among three groups of continent men with PCa undergoing RALP from whom consent was obtained. Each group consisted of 30 patients: PRAS was performed in group A, combined MULP and PRAS in group B, and MULP in group C. Continence was measured by patient self-reporting of the number of pads/24 h.

Results: No differences were detected in the age, preoperative PSA levels, biochemical recurrence, prostate volume, and positive margins for the three groups. Men in groups B and C had marked improvement in CR 1, 3, and 6 months after catheter removal vs. group A (50% and 70% vs. 10%, 90% and 96.66% vs. 23.3% and 100%, 100% vs. 53.3%, respectively, P< 0.0001). The average and median times to continence were significantly shorter in group B (5.4 and 4 weeks) and C (3.8 and 3 weeks) vs. group A (27.4 and 22.5 weeks), P< 0.00001. Using Cox regression analysis, only MULP and MULP+PRAS techniques were significantly correlated with continence outcomes 1, 3, and 6 months after catheter removal.

Conclusions: MULP rather than PRAS confers higher postoperative CR and shorter time to achieve continence among patients with PCa who underwent RALP without increasing risk of positive margin.

HIGH INCIDENCE OF PREDOMINANT GLEASON PATTERN 4 ASSOCIATED WITH LOW SERUM TESTOSTERONE LEVEL IN LOCALIZED PROSTATE CANCER: AN UPDATE WITH 937 PATIENTS

Prostate specific antigen (PSA) lacks many qualities of an ideal testing marker. That said, it can be difficult to escape its application when evaluating males for prostate cancer, and it has some proven utility in treatment decisions. Work in recent years has focused on bolstering the utility of PSA through the use of additional measures, or adjusting its use and how it's reported. In this study, Neuzillet and colleagues report on a prospective study evaluating the association of total testosterone with prostate cancer aggressiveness. The aggressiveness of the cancer was measured using predominant Gleason pattern.

It was performed over approximately 2.5 years for men referred for radical prostatectomy (RP). The biopsy and tissue specimens were analyzed by two uropathologists. A total of 937 men were enrolled. Of these, 139 with total testosterone (TT) <3.0 ng/mL had a higher mean weight and BMI than the rest of the cohort (p <0.001 for both). They observed a predominant Gleason pattern of 4 (prdGP4) in 169 (18%) of biopsies and 290 (31%) of prostate specimens after RP. They found that men with prdGP4 had a lower TT when compared to men with prdGP3 (4.4 vs. 4.7 ng/mL, p=0.017) and had a higher PSA (10.2 vs. 7.7 ng/mL, p <0.001). Additionally, they observed extraprostatic extension and positive margins more often in the cohort of men with prdGP4 (55% vs. 23%, p <0.0001).

These results implicate that the TT has a strong association with prdGP4, which cannot be accurately measured using prostate biopsy. Thus, TT may be useful in adjusting PSA and biopsy results to inform a more detailed and specific decision algorithm. Development and validation of such a decision instrument is an interesting hopeful future for this work. However, additional studies regarding the predictive validity of TT and further studies on the measure would be necessary before such an instrument could be implemented and evaluated.

Presented at the 2014 AUA Annual Meeting, 18 May 2014

Written by Martin Hofmann, MD
Medical writer for UroToday.com

BECKMAN COULTER'S PHI NAMED IN NCCN GUIDELINES AS A RECOMMENDED DIAGNOSTIC TEST FOR EARLY PROSTATE CANCER DETECTION

Beckman Coulter's Prostate Health Index (phi) has been recommended by the National Comprehensive Cancer Network (NCCN) as a blood test to improve specificity for prostate cancer detection in its recently updated Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer Early Detection. Inclusion in the NCCN Guidelines recognizes the benefit and clinical utility of phi for prostate cancer diagnosis and for the reduction of unnecessary biopsies.

"It is exciting to see phi recommended in the NCCN Guidelines. I started offering phi to my patients this year and it has proven to be a valuable addition to our shared decision making process," said William Catalona, MD, principal investigator on the Prostate Health Index clinical study, and urologist at Northwestern Medicine and director of the Clinical Prostate Cancer Program at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University in Chicago.

Approved for use by FDA in men with PSA values between 4 and 10 ng/mL, phi is a simple, non-invasive blood test that is three times more specific in detecting prostate cancer than PSA alone, decreasing the need for many men with elevated PSA levels to undergo a biopsy in order to achieve a reliable diagnosis.

Following the initial testing to detect prostate cancer – PSA and digital rectal exam – the guidelines recommend the use of phi to further define the probability of cancer before undergoing biopsy or a repeat biopsy. It is recommended that tests which improve specificity, such as phi, be considered for patients who have a higher risk of cancer, despite a negative biopsy. The new version of the guidelines is designed to reduce unnecessary testing and over-diagnosis.

"NCCN provides physicians with useful guidelines for prostate cancer detection and treatment," said Dr. Stacy Loeb, assistant professor at the Department of Urology and Population Health at NYU Langone Medical Center in New York and phi pivotal study investigator. "The inclusion of phi addresses the need for a test with increased specificity for clinically significant prostate cancer."

Press Release, Beckman Coulter

16 May 2014

ORTERONEL DELAYS DISEASE PROGRESSION IN ADVANCED PROSTATE CANCER

Orteronel, an investigational oral therapy for prostate cancer, improved progression-free survival, but did not significantly improve overall survival in patients with chemotherapy-naive metastatic castration-resistant prostate cancer (mCRPC). The median overall survival of patients treated with orteronel plus the corticosteroid prednisone was 31.4 months compared with 29.5 months for patients treated with prednisone alone (hazard ratio [HR] = 0.9, P = 0.314).

The median radiographic progression-free survival (rPFS) was 13.8 months compared with 8.7 months in the prednisone-alone arm (HR = 0.7, P <0.00001).

The results (abstract #5008) were presented by Ronald de Wit, MD, PhD, of the Erasmus MC Cancer Institute in the Netherlands, at the American Society of Clinical Oncology (ASCO) Annual Meeting, held May 30–June 3, in Chicago.

The ELM-PC 4 phase III international trial randomized 1,560 prostate cancer patients to either 400 mg of orteronel plus 5 mg of prednisone twice daily or placebo plus prednisone.

A higher proportion of patients had a greater than 50% decrease in prostate-specific antigen (PSA) levels in the orteronel treatment arm compared with the control arm (43% vs. 25%, P < 0.00001). Patients treated with orteronel also had favorable circulating tumor cell counts compared with those in the control arm at 12 weeks on the study (15% vs. 9%, P = 0.00016).

Adverse events that were more common in the orteronel arm included nausea, fatigue, constipation, and diarrhea. More patients discontinued therapy in the orteronel arm compared with the control arm (30% vs 18%, respectively).

Forty-five percent and 51% of the orteronel-treated and control patients, respectively, went on to receive subsequent approved prostate cancer therapies including docetaxel, abiraterone, or enzalutamide.

The previously reported, phase III ELM-PC 5 trial of orteronel plus prednisone in previously treated mCRPC patients also showed an improvement in rPFS but not overall survival for men treated with orteronel.

According to Robert Dreicer, MD, MS, of the Taussig Cancer Institute at the Cleveland Clinic Lerner College of Medicine, and an author of the study, although there was previously clear evidence that orteronel was an active agent in prostate cancer, there was no prior evidence that orteronel could improve survival in chemotherapy-naive prostate cancer.

Orteronel is being developed by Takeda Pharmaceuticals and is a reversible inhibitor of 17,20-lyase, an enzyme involved in the production of androgens. The agent is a second-generation 17,20-lyase inhibitor, similar to abiraterone acetate, another 17,20-lyase inhibitor already approved for the treatment of men with metastatic prostate cancer.

"Many factors may have contributed to missing the objective [of this study], including subsequent therapy or the potential that orteronel is not as active a lyase inhibitor as abiraterone," said Dreicer.

"In the context of several active therapies for metastatic prostate cancer, overall survival is becoming a challenging endpoint to achieve," said Michael Morris, MD, associate professor at the Memorial Sloan-Kettering Cancer Center in New York, who was not involved in the study. "The environment in which we can actually see a survival advantage in any drug is becoming more difficult," said Morris. 'The outcomes really depend in many cases on the therapy patients in the trial cross over to receive after the clinical trial is completed. Whether or not this result is truly reflective of the drug activity is not clear.'

Cancer Network, 3 June 2014

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

"Hey, the U.S. is number one, but in this case it is a very bad thing?! "

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:

Arguably the largest review ever published on the prevalence of obesity around the world over the past 30 years just demonstrated that the U.S. is leading the way in the numbers of individuals who are obese (13% of the global total-yikes!), but the rest of the world is catching up quickly.[1] It is time to treat this as the number one health problem in America and probably the number one health problem in men with prostate cancer. Oh, and tell your friends in the Mediterranean region and anywhere else you think some "healthy" populations are a lot healthier than the U.S. that in time they will be just like Americans so we share in this epidemic together folks!

I can easily eliminate any feelings of happiness you are experiencing today by discussing the new obesity global report that was funded by the Bill and Melinda Gates Foundation. Ouch and Double Ouch! Most striking to me is how the U.S. has been the poster child for the obesity epidemic but today almost every country deserves to be on this new poster. Even Italy has an overweight and obesity prevalence of almost 60% now and France is close behind (perhaps it is the new Mediterranean Super-Size diet?). No country is really immune from this problem anymore and no country over 33 years has seen a significant drop in obesity from this new report! I also find it fascinating that the country that spends the most money on individual birthday candles… aka the country with the longest current life expectancy (Andorra) has a less than 10% obesity rate compared to basically 33% for the U.S. (coincidence? – I think not). Additionally, I find it quite fascinating there has been no shortage of finger pointing at the food industry and other piñatas that you or anyone else can take a shot at right now to help diffuse your anger! Heck, step right up! Wack! Ahh, that feels better! What a freakin' (that is not a swear word folks) waste of valuable time and space.

The point here is that it is still not taken seriously on so many levels that ALL OF US have a responsibility in changing the numbers in a minor way. Health care professionals need to embrace and emphasize weight reduction as much as any procedure or prescription pill. Patients/all individuals need to embrace a full commitment to this cause that places more emphasis on this epidemic compared to more trivial health hazards such as cell phones and brain tumors, artificial sweeteners and cancer, chemicals in drinking water, vitamins/herbs that fight prostate cancer, or the latest on arsenic and rice. It has become quite clear to me that weight/waist gain not only increases the risk of aggressive prostate cancer or recurrent disease, but certainly also increases the risk of the number one cause of death in the U.S. (cardiovascular disease).

Finally, we all need to be more sympathetic and not so hard on ourselves and remember that life expectancy has doubled since 1900 and America is a nation that is quitting tobacco, which was a major metabolic advantage. We will continue to slow this obesity epidemic over the next decade but to reverse it will require a concerted effort and it will not be easy, but then again anything worthwhile is always a pain in the gluteus maximus. And, the next time someone tells you at a cocktail party that they just came from Europe or Asia or another non-U.S. location and everyone there is so much skinnier compared to Americans you should correct them immediately by referring to this latest research article. We are all in this boat together now folks, and the boat is sinking deeper in the water but it is far from sunk (I love ship and water analogies almost as much as I love a good jog several hours after eating ice cream and/or chocolate).

Reference:

1. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 28 May 2014 [Epub ahead of print].

CHEMOHORMONAL THERAPY

(Continued from page 1)

therapy was given at the investigator's discretion upon evidence of disease progression.

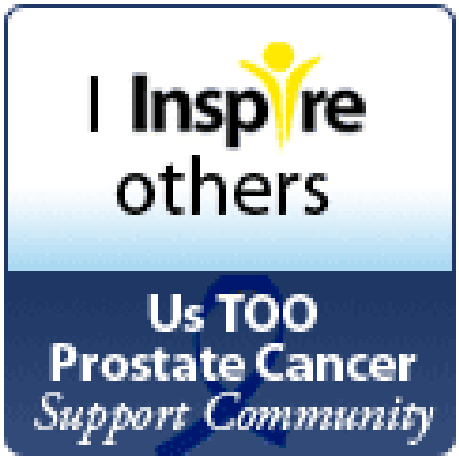
A planned interim analysis in October 2013, at 53% information accrual, met the criteria for significance and release of the study data. Median OS was 57.6 months in the ADT plus docetaxel arm and 44.0 months in the ADT arm (hazard ratio [HR] 0.61; p = 0.0003).

In men with high-volume disease, median OS was 49.2 months with docetaxel plus ADT, compared with 32.2 months with ADT, a difference of 17 months (HR 0.60; p = 0.0006). In men with low-volume disease, median OS had not been reached at the time of the analysis.

Regarding toxicity, 6% of men receiving the chemohormonal regimen experienced fever with lowered white blood cell count, 1% experienced a significant effect on sensory nerves, 1% on motor nerves, and 1 of the 397 patients who received early docetaxel died as a result of treatment.

Commenting on the significance of the study, 2013-2014 ASCO President Clifford A. Hudis, MD, FACP, noted that, "across all solid tumors, this is an almost unprecedented improvement in median survival."

ASCO Daily News, 1 Jun 2014



MORE AGGRESSIVE TUMORS DETECTED WITH TARGETED PROSTATE BIOPSIES *(Continued from page 1)*

"These findings are important as AS is a growing trend in this country," said senior author Leonard Marks, MD, Professor of Urology and Director of the UCLA AS Program. "It's touted as the best course for many men thought to have slow-growing cancers. But we show here that many thought to be candidates for AS based on conventional biopsies really are not good candidates."

Dr. Marks and his team identified 113 men enrolled in the UCLA AS program meeting the criteria for low-risk cancers based on conventional biopsies. Study volunteers underwent an MRI to visualize the prostate and any lesions. That information was then fed into the Artemis device, which fused MRI pictures with real-time, three-dimensional ultrasound, allowing the urologist to visualize and target lesions during the biopsy.

"Prostate cancer is difficult to image because of the limited contrast between normal and malignant tissues within the prostate," Dr. Marks said. "With the Artemis, we have a virtual map of the suspicious areas placed directly onto the ultrasound image during the biopsy. When you can see a lesion, you've got a major advantage of knowing what's really going on in the prostate."

Of 113 volunteers enrolled in the study, 41 (36%) were found to have more aggressive cancer than initially suspected.

"The findings should result in a reevaluation of current AS criteria, Marks said. "We are hesitant now to enroll men in AS until they undergo targeted biopsy. Fusion biopsy will tell us with much greater accuracy than conventional biopsy whether or not they have aggressive disease."

"For men initially diagnosed with low-risk prostate cancer, MRI-ultrasound confirmatory biopsy including targeting of suspicious lesions seen on MRI results in frequent detection of tumors," the study authors stated.

The ASCO Post, 21 May 2014

IMMEDIATE VS. DELAYED ADT *(Continued from page 1)*

Following definitive treatment with surgery (RP) or radiotherapy (RT), a substantial proportion of men subsequently have a rise in PSA level above a critical threshold, even though they remain clinically asymptomatic. BCR causes considerable anxiety for many men.

"Most men and their doctors prefer to begin ADT at BCR. Whether that strategy delays disease progression or improves survival has not been proven," Garcia-Albeniz said. The question deserves an answer because ADT is associated with a variety of adverse effects that diminish quality of life.

The ASCO guideline on the issue states that "the critical issue is to determine whether there is benefit – and how large it is – for starting ADT while patients are asymptomatic." The National Comprehensive Cancer Network guideline characterizes the timing of ADT as a "therapeutic dilemma."

To investigate ADT timing, Garcia-Albinez and colleagues retrospectively reviewed data for 2,022 men registered in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database. All men were treated for localized prostate cancer with either RP or RT, and their PSA values had subsequently risen beyond 0.2 ng/mL, the level used to define BCR.

Investigators grouped the patients according to the timing of ADT. Immediate ADT was defined if given within 3 months of BCR, whereas deferred ADT was defined if given after symptoms developed, after metastasis were detected, if the PSA doubling time was short, or if given ≥2 years after BCR. The primary endpoint was overall survival. The study participants had a median age of 69, a third had received RT as primary treatment for prostate cancer, and the median time from primary treatment to BCR was 27 months.

After a median follow-up of 41 months, 176 men had died, including 37 who died of prostate cancer. Comparing immediate vs. deferred ADT resulted in a nonsignificant survival hazard ratio (HR) of 0.94 (95% CI 0.51-1.73).

Prostate cancer-specific survival associated with immediate ADT was 93.3% at 5 years and 89.4% at 10 years. Corresponding values for deferred ADT were 96.0% and 90.2%. Comparison of immediate vs, deferred ADT resulted in a HR of 1.15 (95% CI 0.33-3.97).

"Finding an answer to the dilemma of ADT timing has implications for about 60,000 men each year who have BCR after definitive treatment of localized prostate cancer," said ASCO President-Elect Peter P. Yu, MD, of the Palo Alto Medical Foundation in California.

"Up to now we have not had evidence that delaying ADT until there are more objective signs of disease is a safe thing to do," said Yu, who was not involved in the study. "This study will provide us with information to have a dialogue between doctors and patients about whether they should start immediate hormone, or whether continued observation and waiting might be a better approach."

Presented at ASCO 2014, Abstract 5003

MedPage Today, 14 May 2014

CHARACTERIZING THE DOMINANT/INDEX LESION IN PROSTATE CANCER: IMPLICATIONS FOR GRADING AND STAGING

Several factors are considered in estimating a prognosis after radical prostatectomy. Some evidence has suggested that the index lesion will have both the highest tumor volume as well as the greatest Gleason score (GS), and will serve as the stage-defining tumor. Dr. Kazuhiro Matsumoto and colleagues, feeling that not enough had been evaluated in this regard, undertook a study to further evaluate these factors. Thus, they presented work on determining how well the tumor volume, highest GS, and stage are associated with the index/dominant lesion in the prostate.

They performed a study of 66 whole-mounted and entirely submitted RP specimens, and for each case, calculated the tumor volume, GS, and pathologic stage for each tumor. Their aim was to calculate the number of cases in which the index tumor was indeed the largest with greatest GS and stage (congruous) and to compare that with the number of

(Continued on page 8)

Want to learn more about local prostate cancer support group activities? Read the

CHAPTER NEWS!

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GENE TEST FOR PROSTATE CANCER VALIDATED: TRIUMPH OR WORRY?

A commercially available prostate cancer test (Prolaris, Myriad Genetics) has been "validated" in its ability to predict disease-specific death in the largest study of its kind, according to a presentation here at the American Urological Association (AUA) 2014 Annual Scientific Meeting. The 46-gene test is marketed as a molecular prognostic tool that assesses the aggressiveness of an individual patient's cancer.

The study showed that the test can differentiate men at higher risk for death from prostate cancer from those at lower risk. But the usefulness of Prolaris – and genetic tests like it – is unclear because it has not yet been demonstrated that it actually improves outcomes, according to a number of experts interviewed.

"For instance, the Prolaris test can indicate that a 60-year-old man with a Gleason score of 7 has a greater risk for metastasis and death than a similarly aged man with the same Gleason score," explained Stephen Jones, MD, from the Department of Urology at the Cleveland Clinic, who was not part of the study. "That may be accurate, but what is the impact on actual outcomes? We don't know," he told Medscape Medical News. "The impact on outcomes is the part that is not validated."

"The study assessed data on 761 men from the United Kingdom who had prostate cancer diagnosed with needle biopsy from 1990 to 2004 and who were conservatively managed with watchful waiting. Definitive treatment was provided at the onset of symptoms. The primary end point of the study was disease-specific mortality (18%), and the median follow-up was 9.5 years," said lead author Jack Cuzick, PhD, from the Wolfson Institute of Preventive Medicine in London, United Kingdom.

Tumor tissue from this prospective cohort was later retrospectively analyzed with the Prolaris test. Thus, the researchers were able to associate outcomes with test scores. The results indicate that for each 1 unit increase in Prolaris score, patients had approximately twice the risk of dying from prostate cancer over 10 years (see table).

Prolaris score	10-year mortality (%)
<0.0	7
1.1 – 1.0	15
1.1 – 2.0	36
>2.0	59

Overall, the test scores are "highly predictive" of disease-specific mortality ($P = 3.9 \times 10^{21}$), according to the study authors. However, Dr. Jones questioned the time period used in the study and the population. "The data may or may not apply to a contemporary group of patients in a different geography – for instance, the United States in 2014. We don't know," he said. Dr. Jones and another expert not involved with the study, Michael Blute, MD, both believe that more studies are needed.

"The test needs to show consistency in a clinical setting," stated Dr. Blute, who is chief of the Department of Urology at the Massachusetts General Hospital in Boston. He said he would like to see prospective multi-institutional clinical trials to reproduce the results in the US. "However, do not expect Myriad to run such trials," said Dr. Brawer, citing expense. "Furthermore, current data provide prognostic information beyond that of standard clinical measures, and are, as such, very valuable," he explained.

Dr. Blute is not opposed to Prolaris or other genetic tests. "A test like this is sorely needed," he said, but too many questions about "clinical utility" remain. Dr. Jones agreed: "It's important that we continue to investigate all of these tests to determine if they are going to give meaningful and actionable information."

The AUA and other organizations need to provide direction, suggested Dr. Blute. "Leadership in urology needs to come to the fore. How are we going to handle tests like this?" he asked. "We don't want the marketing to get out in front of the science. We have seen that in medicine before."

But the marketing has begun for these genetic tests, which include Prolaris, Decipher (GenomeDx), and the Oncotype DX (Genomic Health). And they are expensive, say experts. The list cost for Prolaris is $3400 and for Oncotype DX is around $4000.

Prolaris "is an expensive test," Dr. Brawer acknowledged. But he cited a study that found that the test "changes management in two-thirds of patients." Cost-effectiveness studies are forthcoming. "The savings from preventing under- and overtreatment in some men needs to be assessed when discussing cost," he said.

2014 AUA meeting, abstract MP79-17

Medscape Medical News, 22 May 2014

NADIR TESTOSTERONE ON ADT PREDICTS TIME TO CASTRATE RESISTANT PROGRESSION: A SECONDARY ANALYSIS OF THE PR-7 INTERMITTENT VS CONTINUOUS ADT TRIAL

The NCIC/SWOG/UKCCR PR7 study randomized patients with biochemical failure after radiation or surgery plus radiation and no metastases between continuous lifelong androgen deprivation and intermittent androgen deprivation. The trial showed no difference in overall survival or cancer-specific survival (CSS) between continuous and intermittent ADT. The authors hypothesized that in patients on continuous androgen deprivation, higher testosterone (T) values correlate with a reduced time to development of castrate resistant prostate cancer (CRPC) and lower CSS. Using 626 patients in the continuous ADT arm of the PR7 trial, the relationship between T and the time to androgen independent progression (PSA >4 with T <3nm/L) was examined.

Among the 3 groups (median T <20, 20-50, and ≥ 50 ng/dL), there was a significant difference in time to hormone resistance: CRPC being not reached, 6.4 years, and 4.2 years for the 3 groups respectively. Patients with T >20ng/dL were at significantly increased risk of developing hormone resistance (HR 1.9 for T ≥50 ng/dL). In men with a higher median T level, there was a shorter time from hormone resistance to PC death.

Researchers concluded that low nadir serum T on ADT (<0.7mMol/L or <20ng/dL) correlates with improved duration of response to ADT in men on continuous ADT for biochemical recurrence. ST should be checked regularly in such patients and ADT modified to ensure levels <20ng/dL are achieved.

Presented at the2014 AUA Annual Meeting, 21 May 2014

Jeffrey J. Tomaszewski, MD, medical writer for UroToday.com

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 One long-standing dilemma for patients with a rising PSA after local therapy is when to begin androgen deprivation therapy. Anxiety is probably the driving reason why so many men initiate it early. Unfortunately, a prospective randomized study has never been performed. Now a new uncontrolled study suggests that it makes no difference whether ADT is started early or delayed; the study found no significant difference in overall or cancer-specific survival. However, like so many other studies discussed in this column, this study does not provide a definitive answer to the question. The reasons are in part because the deferred treatment was based on more than one criterion, which included the development of symptoms, metastases, a short PSA doubling time, or metastases more than two years after biochemical relapse. The varying definitions could greatly impact on the overall results. For now, the decision to initiate therapy must be individualized balancing side effects vs. the psychological benefit of seeing the PSA decline.

The Bottom Line: The optimal timing for beginning ADT when a PSA rises in the absence of metastatic disease remains unclear.

a2p1c2 Since the approval of Taxotere back in 2002 for men with metastatic prostate cancer, its use has been delayed until very late in the disease because of concerns about side effects and a small improvement in overall survival. Now a landmark study is likely to change many people's attitude. The study compared ADT to ADT plus chemotherapy for up to six months. Men getting the combination had a 13-month longer overall survival and a significantly reduced risk of death due to prostate cancer. Importantly, the incidence of serious side effects was very low. This study has one very important implication. It means that urologists need to refer men with newly diagnosed metastatic disease to an oncologist for a consultation about adding the chemotherapy. It also means that urologists should become familiar with the findings of the study to insure that men are offered the opportunity for this improved survival.

The Bottom Line: Men with newly diagnosed metastatic disease should be offered chemotherapy along with their ADT to maximize their survival.

a3p1c3 Another major controversy in urology is identifying men who are good candidates for active surveillance (AS). Criteria continue to evolve with some doctors recommending the addition of MRI for making the decision. A new study presented from UCLA combined the MRI with ultrasound in a system called Artemis. The additional target biopsies found more than one-third of men thought to be good candidates for AS really had more extensive disease and should not do AS. While these findings are encouraging, they do not really answer the question whether this test is necessary. The longest and largest series to date on AS did not use this approach and it has found that about one-third of men ultimately end up with definitive therapy. Are these the same men who are being identified using the MRI? That question needs to be answered before determining the added value of this approach. Many doctors are questioning whether the criteria for AS are becoming increasingly too restrictive and will result in too many men getting unnecessary treatment. Referring back to the Scandinavian trial of surgery vs. watchful waiting, at 15 years about 1 out of 8-9 men benefit from surgery and for men over 65 little benefit was seen. This suggests that many more men should be considered for AS since they are not benefitting from treatment. And yet the proportion of men selected for AS is far below this rate. Hopefully, this work will continue to improve so that we really know the natural history of the men who are being omitted from AS.

The Bottom Line: More information is needed to know if the criteria for MRI guided biopsy to select men for AS are too restrictive meaning too many men may get unnecessary treatment.

a4p2c2 One of the persisting problems with radical prostatectomy is urinary incontinence. Over the years, various techniques have been used to try and limit the problem and accelerate recovery. Another new one was presented in a small, prospective but non-randomized study comparing maximum urethral length preservation (MULP) to posterior urethral reconstruction and anterior bladder suspension (PRAS). The authors found a significantly better outcome in terms of time to continence and complete improvement with the better result occurring in men getting the combination or only the MULP approach. If this study is validated in other larger trials, it may offer men better outcomes.

The Bottom Line: Performing MULP during bladder reconstruction may offer men improved urinary continence after radical prostatectomy.

a6p3c1 If a man has a negative prostate biopsy, does he need another one to be sure that cancer was not missed? For many years, the free PSA was used as a secondary test to help make that decision in some men. Another test that has been approved is the Prostate Health Index test (phi) that measures the percent free PSA, and a subcategory of free PSA called pro-PSA. It appears to offer an improved ability to determine which men can avoid another biopsy although it will mean that a small number of cancers will be missed.

The Bottom Line: The phi test appears to help determine which men do not need a second biopsy if their first one is negative.

a10p6c1 Everyone now knows that prostate cancer is not always a lethal cancer and much of the controversy surrounding screening is finding and treating men who are not at risk. Extensive work on gene testing is underway to help in the decision process. The Prolaris test was recently presented at the AUA. It provides a number that presents patients with their odds of dying from their disease in the next ten years. Although the study found that the test result would lead doctors to change their recommendation in many cases, questions still remain. For example, take a patient whose combination of PSA, Gleason score, and DRE result suggests a ten-year mortality of 10% but the gene test indicates it is closer to 15%. How often would a small change in this risk lead to a change in management? Similarly, if a man has a high-risk cancer based on PSA, Gleason score and DRE, would he really consider not being aggressive and would the gene test result

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DOMINANT/INDEX LESION

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cases in which the index tumor was not found to have the highest volume and greatest GS and stage (incongruous).

Ultimately, they found that in 82% of cases, the index tumor was indeed the largest, exhibited the highest GS, and defined the pathologic staging of the cancer. That said, they elaborated on the incongruous cases, with one-third exhibiting a maximum GS in non-index nodule that was >1 GS higher than the index nodule. Similarly, they found that the stage-determining nodule may not have the largest TV or highest GS. This study implies that some changes to analysis and reporting of pathology results may need to be made in order to improve the diagnostic accuracy of studies meant to inform prognosis.

It will be interesting to see this work expanded to include patients for whom follow-up data has or is being collected, and to begin to test the utility of these data in performing more sensible analyses of prostate specimens.

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Written by Martin Hofmann, MD
Medical writer for UroToday.com

DOCTOR CHODAK'S BOTTOM LINE

(Continued from page 7)

change his decision? Ultimately, these types of tests may help some men decide what to do but many experts believe more information is still needed.

The Bottom Line: Gene testing for predicting outcomes are continuing to improve but uncertainty remains whether or not these tests are ready to be used routinely at this time.

a11p6c3 Does the testosterone level achieved during ADT really matter? This important question has never been studied properly even though years ago a small, uncontrolled study suggested it was extremely important. Now, good information is provided from a randomized study that was done comparing intermittent and continuous therapy in men with a rising PSA and non-metastatic disease. The authors looked at the men getting only continuous therapy and found that achieving a testosterone level below 20 ng/dL was significantly better than a level of 20-50 ng/dL and the poorest survival was obtained in the level was above 50 ng/dL. These findings have two very important implications. First, it means that regular testosterone monitoring is a must for men getting ADT. Second, it suggests that changing treatment should be considered for men whose testosterone level is not below 20 ng/dL. The value of changing therapy is not really known at this time and will require a carefully controlled study. Until then, however, men should at least be offered a change in therapy to lower their testosterone level. That could either be a switch to a different LHRH medication (agonist or antagonist) or undergoing an operation to remove the testicles.

The Bottom Line: Achieving a testosterone level below 20 ng/dL for men with non-metastatic disease and a rising PSA after local therapy appears to offer a significant survival advantage compared to men with higher serum testosterone levels.

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