Adjuvant Docetaxel No Help in High-Risk Prostate Cancer

Similar Rates of Progression at 10 Years in Androgen-Dependent Disease

Men with high-risk, nonmetastatic prostate cancer (PCa) saw no survival advantage and no delay in metastases with the addition of adjuvant docetaxel to androgen deprivation therapy (ADT), a randomized trial found.

With a median follow-up of over 10 years, the time to radiologic progression was 8.9 years for ADT plus docetaxel compared with 9.0 years for ADT alone (HR 1.03, 95% CI 0.74-1.43) in a patient population with androgen-dependent disease, according to researchers led by Stéphane Oudard, MD, PhD, of Georges Pompidou Hospital in France.

Based on these results, “docetaxel may not be as suitable in a high-risk setting as in a metastatic setting,” they concluded from their study published online ahead of print in JAMA Oncology.

Men assigned to adjuvant docetaxel had a non-significant 15% improvement in PSA relapse, the study’s primary endpoint. With a median follow-up of 30.0 months, the median PSA progression-free survival (PFS) was 20.3 months for the combination arm compared with 19.3 months for ADT alone (Hazard Ratio [HR] 0.85, 95% confidence interval [CI] 0.62-1.16, P=0.31, not a statistically significant difference).

The phase III trial included 254 men with androgen-dependent, nonmetastatic PCa with rising PSA levels. All men had

(Continued on page 4)

Active Surveillance for Prostate Cancer Can Be Safe for Men Younger Than 60

Active surveillance (AS) is a viable option for select men younger than 60 years who have low-volume, low-risk prostate cancer (PCa), investigators concluded.

In a retrospective study, Adam S. Feldman, MD, of Massachusetts General Hospital in Boston, and colleagues compared 417 men who began AS when they were younger than 60 years with 1,667 who began AS at age 60 years or older. At a median follow-up of 6.2 years, the investigators found no significant difference in five-year rates of biopsy progression-free survival (PFS) in the younger and older men (83% in both), treatment-free survival (74% vs. 71%), metastasis-free survival (99.7% vs. 99%), or PCa-specific survival (100% vs. 99.7%), Dr. Feldman’s team reported in The Journal of Urology (Vol. 201, pp. 1-7, 2019).

In younger men, 131 (31%) eventually underwent treatment, including for pathologic progression in 67% and PSA progression in 18%.

On multivariable analysis, 20% or greater involvement of any core on diagnostic biopsy and PSA density of 0.15 ng/mL or greater were associated with an approximately two-fold increased risk of biopsy progression and progression to treatment, respectively.

“AS is a safe and effective approach which spares any properly selected men younger than 60 years with low-risk PCa from

(Continued on page 4)
Time Interval to Biochemical Failure as a Surrogate End Point in Locally Advanced Prostate Cancer: Analysis of Randomized Trial NRG/RTOG 9202


J Clin Oncol 37: 213-221, 2019

Background: In prostate cancer, end points that reliably portend prognosis and treatment benefit (surrogate end points) can accelerate therapy development. Although surrogate end point candidates have been evaluated in the context of radiotherapy and short-term androgen deprivation (AD), potential surrogates under long-term (24 month) AD, a proven therapy in high-risk localized disease, have not been investigated.

Materials and Methods: In the NRG/RTOG 9202 randomized trial (N=1,520) of short-term AD (four months) versus long-term AD (LTAD; 28 months), the time interval free of biochemical failure (IBF) was evaluated in relation to clinical end points of prostate cancer-specific survival (PCSS) and overall survival (OS). Survival modeling and landmark analysis methods were applied to evaluate LTAD benefit on IBF and clinical end points, association between IBF and clinical end points, and the mediating effect of IBF on LTAD clinical end point benefits.

Results: LTAD was superior to short-term AD for both biochemical failure (BF) and the clinical end points. Men remaining free of BF for three years had relative risk reductions of 39% for OS and 73% for PCSS. Accounting for three-year IBF status reduced the LTAD OS benefit from 12% (hazard ratio [HR], 0.88; 95% CI, 0.79 to 0.98) to 6% (HR, 0.94; 95% CI, 0.83 to 1.07). For PCSS, the LTAD benefit was reduced from 30% (HR, 0.70; 95% CI, 0.52 to 0.82) to 6% (HR, 0.94; 95% CI, 0.72 to 1.22). Among men with BF, by three years, 50% of subsequent deaths were attributed to prostate cancer, compared with 19% among men free of BF through three years.

Conclusion: The IBF satisfied surrogacy criteria and identified the benefit of LTAD on disease-specific survival and OS. IBF may serve as a valid end point in clinical trials and may also aid in risk monitoring after initial treatment.

Prostate Cancer Death Risk Linked to Post EBRT Time to PSA Nadir

Men with a short time to PSA nadir (TTN) and a detectable PSA nadir following external beam radiation treatment (EBRT) with or without androgen deprivation therapy (ADT) for unfavorable-risk prostate cancer (PCa) are at elevated risk of dying from their cancer, investigators concluded.

Among men with a detectable PSA nadir (0.2 ng/mL or higher), those with a TTN less than the median of 12 months had a significant five-fold increased risk of PCa-specific death in adjusted analyses than men who had a TTN of 12 months or more, according to study findings published online ahead of print in the journal Urology. Investigators did not observe this association among men with an undetectable PSA nadir (less than 0.2 ng/mL). The finding could have important disease management implications. “We are excited about this work because it identifies a subset of men at higher risk for PCa-specific mortality who might benefit from early intervention,” lead investigator Luke R.G. Pike, MD, DPhil, of Dana-Farber Cancer Institute and Massachusetts General Hospital in Boston, told Renal & Urology News.

“That is, those patients who have a detectable PSA and a short interval to PSA nadir might thus be selected for more intensive treatment up front, such as with next generation androgensens such as enzalutamide, long before they develop PSA failure or macroscopically visible disease. This should be validated in ongoing clinical trials enrolling men with intermediate risk disease.”

Dr. Pike and his colleagues performed a post-randomization study of men treated in a prospective, randomized, controlled trial that included 204 men with unfavorable-risk PCa (PSA level greater than 10 but less than 40 ng/mL, a biopsy Gleason score of 7 or higher, or MRI evidence of extracapsular invasion, seminal vesicle invasion, or both). The men underwent EBRT to a total dose of 70.2 Gy in 1.8 Gy fractions with or without six months of ADT. Of the 204 men in the study, 113 had a detectable PSA nadir and 91 did not. As part of the study protocol, the team followed patients every three months for two years, every six months for the subsequent three years, and then annually thereafter until time of death or October 9, 2016. After a median follow-up of about 18.2 years, 160 men died, 30 from PCa.

Renal & Urology News
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Doc Moyad’s What Works & What is Worthless Column – Also Known as “No Bogus Science” Column

“Follow Breast Cancer for Diet, Supplements, Lifestyle...? Yes!”

Mark A. Moyad, MD, MPH, University of Michigan Medical Center, Department of Urology

Editor’s Note: Us TOO invites certain physicians and others to provide information and commentary for the Hot SHEET 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.

Over the past 33 years I think I have achieved a darn good prediction record in medicine and medical research (sorry I need this self-verbal boost because I have a fragile ego like most doctors but, of course, not when it comes to football predictions and the whole Michigan and Ohio State thing). Let me reveal one secret indicator to help make sure recommendations are sound and loaded with evidence. Okay...wait for it... “BREAST CANCER RESEARCH!”

Breast cancer research not only gets far more attention, but more research on issues that matter most to me such as diet, supplements or lifestyle changes. Do you ever notice that, in general, whenever breast cancer goes (in terms of reducing side effects for hormone therapy, for example) then several years later, virtually the exact same advice works for men with prostate cancer?! How about the fact that we know now that weight gain, smoking, or being heart unhealthy can increase the risk of breast cancer and breast cancer recurrence... sounds familiar doesn't it?! So this month, when a study of over 2,200 postmenopausal women with non-metastatic breast cancer from Europe was published, it continued to raise my eyebrows even further than they have been massively raised over time. Researchers found that the use of antioxidant supplements with chemotherapy or radiation therapy was associated with an increased risk of overall death and a potential increased risk of breast cancer returning. Some supplements like calcium and magnesium were not associated with an increased risk but, over the entire group, supplement use was NOT correlated with breast cancer prognosis. Hmmm! What?!

Yes, this study is one of many over my career that shouts “less is more” regarding over the counter products for prostate cancer, unless you have to take something with strong clinical evidence. The breast cancer evidence has shown, thus far, that using over the counter products to enhance the effects of chemotherapy or radiation has not been impressive and, in general, does not do much or could have the potential for harm.

This is part of the reason I have not been excited about loading up on supplements after a diagnosis of cancer but rather LOADING UP ON HEART HEALTHY LIFESTYLE CHANGES. In other words, losing some weight, quitting tobacco, moderation or no alcohol, lowering chronic stress, getting better sleep, regular exercise that includes aerobic and resistance activity blah, blah, blah. Getting as heart healthy as you can possibly get has generally been associated with improving cancer prognosis and/or simply living longer and feeling better, but it has not been associated with worse outcomes. In other words, it is a bet where you generally win and never lose (just the mental benefits alone are spectacular), whereas loading up on unproven pills could hurt, or do nothing, and has not yet been associated with benefits. It is interesting that we are now living in an era where active surveillance, for example, is as popular as ever, and treatments, if needed, are as great as ever before. Yet many of us still want some magic, unproven pill on top of this when, in reality, the MAGIC LIES WITHIN YOU!!!

It is far more impressive to work out, eat better, and optimize your heart healthy numbers than it is to learn about the latest and greatest elixir and spend a fortune of your cash on it, not even knowing for sure if it will help, harm or do nothing!

Breast cancer is talking to many of my prostate cancer buddies (some health care professionals) and it is shouting to change some aspect of your lifestyle after a diagnosis, or during or after conventional treatment... Can you hear the shouting? I hope so because, for 33 years, breast cancer has been sending us a clear, loud message that to-day is as loud and as clear as any other time in medicine. THE MAGIC ALSO LIES WITHIN YOU RIGHT NOW!

I apologize but I had a lot of caffeine when I wrote this column!

References:

Fusion Biopsies in Active Surveillance for Prostate Cancer Predict Progression Risk

Men on active surveillance (AS) for prostate cancer who have negative results from a confirmatory fusion biopsy (FB) are at significantly lower risk for Gleason Grade Group (GG) progression. Negative FB findings were associated with a significant 59% decreased risk of GG progression vs. positive findings, investigators led by Peter A. Pinto, MD, of the NCI in Bethesda, MD, concluded in a paper published in The Journal of Urology (Vol. 201, pp. 84-90, 2019).

“A negative FB on AS, which is a powerful indicator of favorable outcomes on AS, can be used to counsel patients regarding the risk of progression,” the investigators concluded. “This information can help urologists decide how often to plan follow-up visits as these patients may be offered longer intervals between subsequent follow-up examinations, imaging and biopsies.” The study included 542 men, 466 patients with GG 1 and 76 with GG 2 cancer based on systematic biopsy. All men underwent FB, which consisted of extended sextant systematic biopsy plus multiparametric magnetic resonance imaging (mpMRI)-transrectal ultrasound (TRUS) targeted biopsy of suspicious lesions found on mpMRI.

Of the 542 men, 110 (21.5%) GG 1 and 10 (13.2%) GG 2 men had negative findings on FB and elected to continue on AS. A total of 224 men (41.3%) were upgraded to a higher GG, including 205 (44%) in the GG 1 arm and 19 (25%) of the GG 2 arm. After initial confirmatory FB, 210 men sought definitive treat-

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undergone primary local therapy for their PCa and were considered at high risk for metastases. Men were randomly assigned to one year of ADT with or without docetaxel.

Men in both arms had a PSA decline of 50% or more compared with their baseline level, with the majority in both arms experiencing this decline by 12 weeks. Overall survival results are not yet mature. All-cause deaths occurred in 32.0% of men treated with docetaxel vs. 36.8% without docetaxel.

In an accompanying editorial, Nicholas J. Vogelzang, MD, of Comprehensive Cancer Centers of Nevada in Las Vegas, wrote that Oudard and colleagues’ results add another layer of whether disease burden is more important than androgen environment “trumps disease burden” when selecting therapy.

“The powerful role that the androgen receptor (AR) and its inhibition plays in earlier-stage disease was not clear in 1999-2003, but is now apparent with the apalutamide and enzalutamide trial results,” Vogelzang wrote. “I believe that it is not until the cancer has evolved to a significant fraction of cells that are independent of AR (and by implication, independent of second-generation androgen-receptor inhibitors) that taxane therapy (either adjuvant or for established disease) improves survival.”

Vogelzang stated this theory would explain the negative results of SWOG S9921 in androgen-dependent, non-metastatic disease PCa, where no advantage was seen with adjuvant mitoxantrone combined with ADT, and the negative results of CHARITED and the GETUG-AFU 15 trial, where adding docetaxel to ADT did not improve survival.

Based on these findings and those from the SWOG trial, Vogelzang currently recommends adjuvant ADT for one to two years in high-risk patients. However, in young patients with node-positive disease and detectable PSA after radical prostatectomy, he does recommend adjuvant taxane therapy based on the idea that disease in these very poor risk patients could see “early evolution to AR independence.”

In general, he noted that adjuvant taxane therapy for low-volume disease should be a “selectively considered” option. “There may be men for whom adjuvant taxane therapy is useful—I simply do not know which ones they are,” Vogelzang said.

Oudard and colleagues conducted several exploratory analyses of baseline attributes and their effect on PSA and radiologic PFS. For PSA PFS, HRs favored combination treatment for all baseline attributes examined. For radiologic PFS, men with more than three high-risk factors had a significantly shorter survival vs. men with three or less risk factors (HR 0.54, 95% CI 0.34-0.86, P=0.008), but no association with treatment was found.

The most common grade 3/4 hematologic adverse effects in the combination arm were neutropenia (a low white blood cell count, 48.0%), febrile neutropenia (8.0%), and thrombocytopenia (a low platelet count, 3.0%).

MedPage Today
31 January 2019

AS for PCa Can Be Safe for Men Younger Than 60 (Continued from page 1)

intervention, provides adequate time for intervention if required, and shows durable disease-specific survival,” the authors concluded.

Unfavorable measures of tumor volume, such as elevated PSA density, percent of positive cores, or percent of tumor involvement per core, “are important factors to incorporate into shared decision making with patients since they may be harbingers of more aggressive disease that would benefit from definitive treatment.”

Patients’ median age in the younger and older groups was 55 and 69 years, respectively. At baseline, men in the younger-than-60 group generally had more favorable disease characteristics than men in the age 60 and older group. For example, the younger group had a significantly lower initial PSA level (4.6 vs. 5.5 ng/mL) and had a significantly greater proportion of men with Grade Group 1 disease on initial biopsy (97.8% vs. 90%) and with clinical stage T1 cancer (93.1% vs. 86.3%).

Dr. Feldman and his colleagues cited a previous study of younger men managed with AS at the University of Michigan in Ann Arbor commented on the findings in an accompanying editorial. “While such findings represent a substantial paradigm shift with regards to the role of age in AS, these analyses further enhance the primary importance of tumor volume metrics such as PSA density and biopsy tumor involvement when risk stratifying patients eligible for active surveillance.”

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28 January 2019

Check out Us TOO web pages on maximizing quality of life after prostate cancer treatment:

Sexual Health/Intimacy & Erectile Dysfunction at www.ustoo.org/intimacy

and Urinary Incontinence at www.ustoo.org/incontinence

AS for PCa Can Be Safe for Men Younger Than 60 (Continued from page 1)
Good Quality of Life But Sexual Dysfunction Common After Prostate Cancer

Overall, men who have been treated for prostate cancer (PCa) can expect quality of life equal to that of men in the general population, even those diagnosed with advanced disease, concludes the largest study of its kind. However, the study also shows that sexual dysfunction is virtually ubiquitous among men treated for PCAs, regardless of age or disease stage. In addition, men treated with androgen deprivation therapy (ADT) frequently report problems with hot flushes, low energy, and weight gain, the study shows. “This study is the largest population-based, patient-reported outcomes study of men with PCa to date,” say the authors, led by Amy Downing, PhD, University of Leeds, UK. The study was published online January 31 in The Lancet Oncology.

Participants in this British study were initially identified by cancer registration data, and were then mailed a health-related quality of life (HRQOL) survey. The questionnaire was completed at 18 to 24 months after diagnosis of PCa. The median age was 71 years and the majority of participants reported having at least one other long-term health problem. The study collected data on 35,823 men with PCa, including 11,000 men living with locally advanced or metastatic disease (stage 3 or 4 disease), who are often excluded from quality-of-life (Qol) studies, the authors note. Disease stage was known for 85.8% of the cohort, out of which 63.8% had stage I or II PCa, 23.4% had stage III disease, and 12.8% had stage IV disease.

To assess functional outcomes, the EPIC-26 (Expanded Prostate Cancer Index Composite short form) was used to measure urinary incontinence; urinary irritation and obstruction; and bowel, sexual, vitality, and hormonal function, whereas the EuroQol (EQ-5D-5L) questionnaire assessed measures of mobility; self-care; the ability to carry out usual activities of daily living; pain or discomfort; and anxiety or depression. The EQ-5D-5L was also used to rate a patient’s self-assessed health based on how good he or she felt on the day the survey was completed.

“Mean adjusted EPIC-26 domain scores were high in all men, indicating good function, except for sexual function, for which scores were much lower,” Downing and colleagues report. Urinary and bowel function as assessed by the same questionnaire was similar across all stages of disease. “In contrast, men with stage 3 and 4 PCa had significantly lower scores for vitality as well as hormonal and sexual function compared with men who had localized disease,” study authors note.

“Not surprisingly, more men who had their cancer removed surgically reported urinary incontinence than men who did not undergo prostatectomy, while men receiving ADT had worse hormonal and sexual function than men not treated with ADT,” investigators add. Among men reporting poor urinary function, “the need to urinate frequently was the most common urinary symptom,” the researchers note. There was little difference in the incidence of this side effect between different stages of PCa, but there was a difference between the different treatments that were administered.

“Almost one third of men in the surgical group reported having to use pads one or more times per day, a higher rate than that reported by men treated with other modalities,” the researchers observe. Importantly, bowel dysfunction was a relatively infrequent complaint, and again differed little by disease stage.

However, of those men who did report bowel problems, more men who underwent external beam radiation therapy (EBRT) alone (or in combination with other modalities) were more affected by bowel urgency than men treated with surgery alone. Problems with low energy, hot flushes, and weight gain were, in contrast, more related to stage of disease than urinary or bowel problems, but rates of these complaints varied considerably depending on how the PCa had been treated. For example, men who received ADT, either alone or in combination with other therapies, were much more likely to report problems with hormonal function and fatigue than men who had not received ADT.

Specifically, over 30% of men receiving ADT reported experiencing significant hot flushes, and a similar percentage of men reported having low energy; these rates were much higher than in men who had not received ADT. Men treated with ADT were also more likely to report weight gain vs. men who had not received ADT. Poor or very poor erections were, on the other hand, an extremely common complaint across the whole population, being reported by 81.5% of the group, with equal percentages reporting poor or very poor overall sexual function. Sexual dysfunction rates were high, even among men with localized disease, although they were higher still among men with later stages of PCa.

Men who reported undergoing active surveillance were the least likely to report poor or very poor overall sexual function yet, even in this group, over half of patients registered this as a major complaint. About 45% of men overall also indicated that they were bothered by their poor sexual function, although this complaint decreased slightly with age.

About 40% of men who reported poor or very poor sexual function noted that they were offered medications, devices, or counseling to help improve their sex lives. However, this meant that close to 56% of the group were not offered any intervention for sexual dysfunction, and this percentage remained relatively high, even in the youngest cohort. Of those offered some sort of intervention, over 37% didn’t bother with any of them and almost one quarter of recipients indicated that the intervention did not help. That said, “the overall mean adjusted self-assessed health score was 76.3,” Downing and colleagues report, “which was only 5.7 points lower in men with stage 4 disease compared with men with stage 1 or 2 PCa.”

As the authors note, most men with stage 3 or 4 PCa in this particular cohort were on long-term or indefinite ADT. Results suggest that clinicians should pursue treatment approaches that preserve testosterone function when possible and minimize ADT use.

Medscape Medical News
5 February 2019
Low Carb Diet and Walking May Ease Adverse Effects of Androgen Deprivation Therapy

Men on androgen deprivation therapy (ADT) for prostate cancer may be able to ease adverse effects of the treatment by adhering to a low-carbohydrate diet (LCD) plus walking, new findings from a small study suggest.

In a randomized trial of 42 men on ADT, those who followed a regimen which consisted of limiting carbohydrate intake to 20 grams per day or less and walking for at least 30 minutes for five days or more – experienced significant weight loss and improved hemoglobin A1c and lipid profiles vs. controls who maintained their usual diet and exercise patterns.

“If confirmed in larger studies, a low-carbohydrate diet may be a good option for men to avoid the side effects of hormonal therapy,” stated lead investigator Stephen J. Freedland, MD, of Cedars-Sinai Medical Center in Los Angeles. “At the least, it is a potent means to lose weight with no clear increased risk of adverse effects due to ADT or no negative effects on PSA control. Future studies are planned to combine a low carbohydrate diet with exercise to see if we can achieve even greater responses.”

For the study, investigators randomly assigned 20 men to the LCD/walking group and 22 men to the control group. The primary outcome was change in insulin resistance at six months.

“At six months, insulin resistance decreased by 4% in the intervention group and increased by 36% in the control group, but the difference was not statistically significant,” investigators reported in Prostate Cancer and Prostatic Diseases. They said the study was underpowered to detect a difference due to a smaller-than-planned study population.

The intervention arm, however, did experience a significant 36% improvement in insulin resistance at three months vs. controls.

Also at three months, men in the LCD/walker group experienced significant weight loss (median 7.8 kg) and a median 3.3% decrease in hemoglobin A1c, 13% improvement in high-density lipoprotein, and 37% decrease in triglycerides compared with controls. At six months, the median weight loss in the intervention arm, relative to controls, was 10.6 kg and median increase in HDL was 27%. The study found no significant difference in PSA levels between the groups.

“In addition to the small sample size, study limitations included an inability to distinguish the effect of the LCD from the walking advice or from weight loss,” the authors noted. Another limitation was early discontinuation due to slow patient accrual. They planned to enroll 100 men, but instead only enrolled 45, of whom three were ineligible or withdrew.

“Some patients refused to participate in the study because they consider dietary intervention as an additional burden,” Dr. Freedland and his colleagues stated. “On the other hand, some refused to participate because of the possibility of being randomized to the control group. Transportation to clinical site due to distance was also a barrier for some.”

Castrate T Levels (Continued from page 1)

of prostate cancer who were treated with ADT and definitive radiotherapy (RT) from 2000 to 2015.

The men were divided into two groups on the basis of their minimum T level during continuous gonadotropin-releasing hormone agonist therapy: <20 ng/dL, and 20–49 ng/dL.

Rose and colleagues report that for men with T levels from 20-49 ng/dL, 10-year biochemical recurrence rates were higher (28.1% vs. 18.3%), as were metastasis rates (12.9% vs. 7.8%), compared to the patients with T levels <20 ng/dL.

The difference in rates persisted when the investigators performed multivariable analyses. Also, shorter-term measures favored the group with lower T levels.

Specifically, a T nadir of 20-49 ng/dL was associated with higher three-month post-RT PSA levels compared to a T nadir <20 ng/dL (P=0.001, a statistically significant difference) and higher two-year PSA nadir (P=0.005, also statistically different).

Higher PSA levels are undesirable and are a sign of more active disease. There was also a trend noted toward inferior prostate cancer-specific mortality for the 20–49 ng/dL group.

“Our study suggests that there are clinically significant differences in early PSA response and long-term clinical outcomes among men who achieve differing levels of T suppression below the historical 50 ng/dL castrate level,” summarize the authors.

“The new results raise questions about current practice and castrate levels of serum T,” suggested David Wise, MD, PhD, a medical oncologist at New York University (NYU) Langone Health in New York City.

“The NCCN [National Comprehensive Cancer Network] guidelines recommend <50 ng/dL, and this is an accepted standard,” he told Medscape in an email.

“This study provides an intriguing pilot dataset that calls into question the reliance on this standard <50 ng/dL threshold,” Wise added.

“The new findings need further validation in an independent cohort,” he advised.

The NYU physician also said that it is standard to check the serum T level after initiation of ADT to ensure appropriate suppression.

“Inadequate T suppression can happen and is a preventable cause of poor outcome,” he reminded.

Wise said the new findings are consistent with previous suggestions of a link between the depth of T suppression and clinical outcome. According to the study authors, the new results also prompt the question of what to do clinically when T levels cannot be satisfactorily suppressed.

“Newer therapies such as abiraterone and enzalutamide may suppress serum T more effectively in many patients and thus hold promise as adjunct therapies in patients with insufficient T suppression,” they propose.

Again, Wise said use of these agents needed confirmation: “Further prospective studies will be needed to validate this approach for this highly curable disease.”

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8 February 2019

Medscape Oncology
24 January 2019
**Doctor Chodak’s Bottom Line**


**Editor’s Note:** Us TOO has invited certain physicians and others to provide information and commentary for the Hot SHEET 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.

**P1, “Does Castrate in...”** How low should the testosterone (T) level drop to get the best result from ADT therapy? Over the years, several studies have addressed this question, but none from a well-done randomized study. In this latest retrospective analysis, Rose and co-workers analyzed 764 men with intermediate- or high-risk prostate cancer who were treated with ADT plus external-beam radiation. They analyzed the results according to the nadir T level achieved on ADT and found a significantly higher biochemical disease-free survival and metastases-free survival in the men achieving a T level less than 20 ng/dL vs. men with a higher T level. Ideally, we would have this concept tested in a randomized clinical study, and it should be done because about 5-8% of prostate cancer patients treated with ADT fail to achieve the lower T level.

**The Bottom Line:** Men who achieve a T level below 20 ng/dL may have a lower rate of disease progression than men with a higher T level, but a randomized study is needed to confirm this observation.

**P1, “Adjuvant Docetaxel...”** There are many strange aspects about managing advanced prostate cancer. Some treatments work well in certain circumstances but not in others, making the choice of what to do quite challenging. The latest finding is that men with higher-risk non-metastatic, hormone-sensitive disease do not benefit from adding one year of docetaxel when they begin androgen deprivation therapy (ADT). This is in contrast to newly diagnosed metastatic disease where survival improved when docetaxel was used with ADT. Although the study is not completely mature, data collected thus far show that the death rate is not significantly different. Interestingly, the editorial comment recommends adding docetaxel for men with positive lymph nodes or a measurable PSA after radical prostatectomy, even though it is unclear whether this approach would lead to an improved outcome. We would need another randomized trial to find out if these men do benefit from docetaxel.

**The Bottom Line:** Adding one year of docetaxel to ADT does not appear to benefit men with high-risk non-metastatic disease.

**P1, “Active Surveillance...”** The good news for men considering active surveillance (AS) is that new information is regularly being reported. The latest is a retrospective study comparing outcomes in men younger than 60 years old. In many centers, doctors are uncomfortable promoting AS to younger men out of fear that their prostate cancer will progress. However, this study found a similar rate of progression in both groups. Unfortunately, the median follow-up was short (about six years), which doesn’t allow a valid comparison of outcomes from the two groups. In multivariate analysis, researchers showed that a PSA density of 0.15 ng/mL2 or greater and any biopsy showing 20% cancer in any one core was associated with a significantly higher rate of progression. These two factors may be worth considering if a younger man is interested in AS. We still need a randomized study to truly determine if younger men are at greater risk.

**The Bottom Line:** Men under 60 can still be offered AS unless they have a PSA density of 0.15 or greater or a single biopsy core with more than 20% cancer, but randomized data are needed to confirm this finding.

**P2, “Time Interval to ...”** One of the challenges with prostate cancer research is the long period needed to see survival results, the gold standard for evaluating outcomes. Finding an interim outcome that reliably predicts survival could be of great help. New data from a randomized trial evaluating long and short-term androgen deprivation found that biochemical failure was a significant predictor of death and might be a useful way to analyze new studies. Here is a thought, however: To truly understand the reliability of an interim marker, we need to be told the true positive and true negative results.

**The Bottom Line:** Biochemical disease-free survival may be a useful interim marker for predicting survival but more data are needed.

**P3/P8, “Biopsies... MRI...”** Is MRI a more reliable way to perform a biopsy than random ultrasound guided biopsies? A randomized study of 273 men from Canada compared ultrasound guided biopsies to MRI plus ultrasound guided biopsies and found that each missed about the same number of significant cancers and the frequency of upgrading to Gleason Grade 2 was similar in the two groups. They concluded that both should be used when performing a confirmatory biopsy. A second study by Pinto, et al., found that a negative fusion biopsy was a useful way to select the right patients for AS.

**The Bottom Line:** A fusion biopsy can be used to identify men with Grade Group 2 prostate cancer. However, the study by Klotz suggested that additional information is obtained by performing random biopsies as well.

**P5, “Good Quality of Life...”** What is the actual percentage of men who are adversely affected by their treatment for prostate cancer? The answer is not readily available from the general urological community, al-

(Continued on page 8)

**Resources Address Anxiety, Depression & Prostate Cancer**

Many men who are diagnosed with prostate cancer, or are managing the disease, experience some level of anxiety and/or depression. Caregivers may also be affected. The psychosocial challenges surrounding treatment choices and side effect management can have a negative impact on quality of life.

Anxiety and depression aren’t always effectively treated, in part because the symptoms may not be recognized. We encourage you to visit the Us TOO web page for important information on recognizing and managing anxiety, depression and prostate cancer.

www.ustoo.org/anxiety-and-depression
Adding MRI Does Not Boost Prostate Cancer Upgrading Rate

Magnetic resonance imaging (MRI) with targeted prostate biopsy added to systematic biopsy for men on active surveillance for low-risk prostate cancer (PCa) does not significantly increase the upgrading rate on confirmatory biopsy compared with systematic biopsy alone, according to a new study.

The finding is from a prospective multicenter trial led by Laurence Klotz, MD, of Sunnybrook Health Sciences Centre in Toronto. The trial randomly assigned 273 men with grade group (GG) 1 PCa to undergo confirmatory 12-core systematic biopsy or MRI with targeted biopsy in addition to 12-core systematic biopsy. The primary endpoint was the proportion of men upgraded to GG 2 or higher cancer.

“At the time of confirmatory biopsy, 23% of men in the systematic biopsy group and 21% of those in the MRI group were upgraded to GG 2 PCa or higher,” Dr. Klotz and his colleagues reported online ahead of print in European Urology.

Systematic and targeted biopsies missed significant cancers in 6% and 8% of men, respectively.

“In patients with a higher risk of significant cancer based on clinical parameters, systematic biopsy should be performed, even if the MRI is negative,” the authors wrote. “Our data also suggests that high-risk patients with a positive MRI should have both systematic and targeted biopsies.”

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Dr. Chodak’s Bottom Line (Continued from page 7)

though many specialists have been reporting this percentage for years. The problem, of course, is that doctors in private practice have no incentive to obtain this information, so their patients are only likely to be told about the results from the major centers where many more men are treated. In this British study, about 25,000 men with non-metastatic disease completed a standardized, self-administered survey 18-24 months following diagnosis. In men with Stage I or II disease, 75% reported poor or very poor sexual function. Sexual dysfunction occurred in half the men on active surveillance, but increased to 75% of men treated with surgery. Surprisingly, only about 40% were offered some intervention for their sexual problem. Also, one-third of the men reported using one or more pads per day for urinary leakage. The results for both of these adverse events are much higher than most men are told, which means that many are not truly receiving adequate informed consent. Also, we need to find out why so few men are being offered help for their erection problems.

Fusion Biopsies (Continued from page 3)

ment. The remaining 332 men continued on AS after a negative or positive confirmatory FB.

Of these 332 patients, 182 underwent a subsequent FB. The group included 60 and 122 men with a negative and positive FB, respectively. These patients were followed on AS with a median time to GG progression of 74.3 and 44.6 months, respectively.

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To raise awareness and provide educational resources and support services to those affected by prostate cancer to help them learn to fight this disease. The power of Us TOO is in helping men and those who love them by transforming resignation into determination and fear into hope.

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Us TOO International Prostate Cancer Education & Support

Hot SHEET – MARCH 2019
Between the Sheets...
March 2019

This column provides the platform for experts in the field to help men and women by providing answers to questions about sexual health and intimacy challenges that can result from prostate cancer treatment.

This column was compiled with the help of Dr. Anne Katz, Certified Sexuality Counselor and Clinical Nurse Specialist at CancerCare Manitoba. She has educated thousands of healthcare providers and cancer survivors about cancer, sexuality and survivorship. She is the editor of the Oncology Nursing Forum, an avid blogger for ASCO Connections, and the author of 13 books on the topics of illness, sexuality and cancer survivorship. (www.drannekatz.com)

QUESTION FROM PROSTATE CANCER SURVIVOR:
I’m 68, and have undergone laparoscopic surgery in 2007. I have bladder control 99% of the time. I do not have erections you can count on for sexual function. I was divorced (not for this reason) shortly after the surgery. Alone, a 56 yr. old man does not get terribly excited, and I told myself this was why “my old friend” did not work. I’ve done some work with a therapist who used injections. This was a horrible experience with hardness that actually hurt! In 2015 I met and married a woman who just makes things work for us both. The importance of having a partner to work with is so great, and being single for most of the first three years, I had to wonder if there could possibly be some form of sexual therapy other than prostitution a man in my situation could find, AND afford? However when I was alone, I discovered a trick. By tying a soft cord at the base of my penis, below and including the scrotum, my erection was dependable enough to have sex.

Question #1: Is this something new?
Question #2: Is this something that other men might take advantage of?
Question #3: Am I alone in finding that “therapy” after surgery is not something doctors routinely offer?

RESPONSE FROM DR. ANNE KATZ:
I am happy that you have found someone to share your life with. In answer to your questions about using what we call a “constriction device” to maintain an erection...

A1: This is not something new. Men can use all sorts of constricting devices (soft cord, constriction ring, leather band etc.) for this purpose. It is often called a “cock ring” in lay language.
A2: Yes, of course other men can try this – and many have!
Q3: It depends what you mean by “therapy.” Healthcare providers have specific skill sets; urologists are surgeons and the “therapy” they offer is in the surgical area. Urologists tend to offer pills and injections for erectile problems because this is what they have been trained to do. Sex therapists and counselors view things from a more holistic perspective and are skilled in communication, etc. The key is to find a professional who can provide you the help you need. There is no “one size fits all” approach to the complex issue of male sexuality.

Watch Dr. Katz’ presentation on sexual health and intimacy from the Prostate Cancer Pathways for Patients and Caregivers event recorded at Englewood Health in Englewood, NJ on September 29. 
https://www.youtube.com/watch?v=A2ZdDHw2WGY&t=8542s

Do you have a question about sexual health or intimacy? If so, we invite you to send it to Us TOO. We’ll select questions to feature in future Between the Sheets columns.

Please email your question to: ustoobts@usto.org

Or mail your letter to:
Us TOO International
Between the Sheets
2720 S. River Road, Suite 112
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Advancements in prostate cancer research provide hope for finding a cure and lead to the discovery of new treatments to minimize the impact of a man’s prostate cancer and maximize his quality of life. Us TOO is excited to introduce this new, regular Hot SHEET supplement which includes some of the latest research from the Prostate Cancer Foundation (www.pcf.org).

The PCF is the world’s leading philanthropic organization funding and accelerating prostate cancer research. Founded in 1993, the PCF has raised more than $745 million and provided funding to more than 2,000 research programs at nearly 200 cancer centers and universities.

For the past 25 years, PCF has hosted an annual scientific retreat, which has become the foremost scientific conference in the world on the biology and treatment of prostate cancer. The top five most important prostate cancer research topics or discoveries that were recently presented at the 2018 PCF Scientific Retreat are as follows:

1. Delivering Radiation Directly to Prostate Cancer Cells (and Prostate Cancer Cells Only!)
Traditional radiation therapy can damage surrounding tissue in addition to cancerous tissue. However, a new kind of targeted radiation therapy uses PSMA (Prostate Specific Membrane Antigen), a protein that is found in large concentrations on the surface of prostate cancer cells, to deliver radiation directly to prostate cancer cells in the prostate and those that have metastasized in the body. In PCF-funded studies, Dr. Jeremie Calais (UCLA) and team are testing this treatment in clinical trials and are developing biomarkers to identify which patients are good candidates for this treatment, and why some patients may or may not respond to it. (Teachable moment: A biomarker is a biological indicator of a disease characteristic, such as treatment responsiveness. For example, the PSA test is a biomarker of potential prostate cancer growth.)

2. New Drug Rucaparib for Some Men with Metastatic Disease
First, a little background: BRCA1/2 gene mutations are found in some men and women with advanced cancer. You might recall it was made most infamous by actress Angelina Jolie who used her breast cancer diagnosis to help raise awareness. We now know that if you are a man with metastatic castrate resistant prostate cancer (mCRPC) and you have a BRCA mutation (~25% of men with mCRPC), a new drug, rucaparib, could be for you. In an ongoing clinical trial led by PCF-funded investigators, rucaparib had encouraging antitumor activity in about 50% of mCRPC patients with BRCA1/2 mutations, and has been granted FDA Breakthrough Therapy status (a process to fast-track FDA review of highly promising drugs).

3. Drugs That Can Treat Prostate and Breast Cancer?
In a search for treatments for triple-negative breast cancer (TNBC), which is highly aggressive and cannot be treated with the hormone therapies used for other types of breast cancer, PCF-funded researcher Dr. Suzanne Conzen (University of Chicago) and team identified a hormone receptor relative, the glucocorticoid receptor (GR), as a promising treatment target. Studies by Conzen and other PCF-funded researchers found that GR may also drive resistance to AR-targeted therapy in some men with prostate cancer. Dr. Conzen and team have developed new GR-targeting drugs, and are testing these in clinical trials for prostate, breast, and other cancers.

4. Reversing Neuroendocrine Prostate Cancer (NEPC)
Neuroendocrine prostate cancer (NEPC) is a highly aggressive and lethal form of prostate cancer that affects ~17% of patients with advanced CRPC. Because this form of prostate cancer is so aggressive, there is an urgent need to develop new and effective treatments for patients with NEPC. PCF-funded researcher Dr. Amina Zoubeidi (Vancouver Prostate Centre) has discovered a “regulator” gene (EZH2) that controls NEPC. When enzalutamide-resistant prostate cancer cells are given EZH2-inhibitors, they revert and become treatable again with enzalutamide. EZH2 inhibitors are now in clinical trials for advanced prostate cancer.

5. Testing a Beta Blocker for Prostate Cancer
In case you don’t know, Beta Blockers are part of a class of drugs that reduce your blood pressure by blocking the effects of adrenaline in your system. So, what do Beta Blockers have to do with prostate cancer? Studies suggest that adrenergic nerves, that is, the ones that require adrenaline to function, may regulate the growth and progression of prostate cancer. Drs. Benjamin Gartrell (Albert Einstein College of Medicine), Paul Frenette (Montefiore Medical Center), and team are investigating the mechanisms of this activity and are testing beta-blockers in prostate cancer clinical trials.

For more information visit www.pcf.org, email info@pcf.org, or call 1-800-757-2873.