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NEW NCCN GUIDELINE SEEKS ‘MIDDLE GROUND’ ON PSA TESTING

Updated guidance from the National Comprehensive Cancer Network (NCCN) seeks to establish a “middle ground” for the use of prostate-specific antigen (PSA) testing in men in the United States, said an official here at the NCCN 19th Annual Conference.

The guidance falls between the extremes of “testing nobody” and “testing everybody,” stated Peter Carroll, MD. The latter, he said, involves “aggressive and repeated screening.” Dr. Carroll is chair of the NCCN Prostate Cancer Early Detection Panel and professor of urology at the University of California, San Francisco. The updated guidance “strikes a nice balance,” he said in an email.

Overall, the guidance, which was previously “very, very complicated,” is now “very much simplified,” added panel member Andrew Vickers, PhD, a biostatistician at the Memorial-Sloan Kettering Cancer Center in New York City. Notably, the guideline recommends routine PSA testing for all healthy men starting at age 45 and continuing, in some cases, past age 70.

That advice represents more of a fringe than a middle ground, suggested a critic.

“The [updated] NCCN guidelines still take a more aggressive stance toward PSA testing than do the recent guidelines

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MAY 2014

ADT NO HELP AS PRIMARY TREATMENT FOR PROSTATE CANCER

Primary androgen deprivation therapy (ADT) offered no survival benefit for men with localized prostate cancer who opted not to have RP or RT, or active surveillance (AS), data from a large retrospective cohort showed. Arnold L. Potosky, PhD, of Georgetown University Medical Center and colleagues published the study online in the *Journal of Clinical Oncology*.

ADT has proven effective as palliative therapy for men with metastatic prostate cancer, and may improve survival in certain settings such as adjuvant therapy for men with lymph node-positive disease treated with RP or RT. However, despite a lack of supporting evidence, ADT has increasingly been used as primary therapy for localized disease.

In an effort to inform decision making about primary ADT, Potosky and colleagues reviewed data from three integrated health plans. They identified men with newly diagnosed clinically localized (T<4) prostate cancer from 1995 to 2008 who had opted not to have definitive local treatment. Follow-up continued through 2010. The primary outcomes of interest were all-cause and prostate cancer-specific mortality.

The analysis included 15,170 men, of whom 3,435 received primary ADT. Men who received ADT were older, had

(Continued on page 6)

PSA SCREENING TESTS DOWN

Physician orders for screening PSA tests began to drop off shortly after publication of inconsistent screening trial results in 2009, accelerating into 2012 when the US Preventive Services Task Force (USPSTF) recommended against routine screening, according to a new report published online in the *Journal of Urology*. By comparison, requests for cholesterol screening tests remained stable throughout the five-year study period.

Much of the controversy about PSA testing revolves around clinical trial results and the USPSTF recommendation, but those are not the only factors. A recent systematic review and meta-analysis found no evidence that PSA screening reduces prostate cancer-specific mortality. Another study found that PSA screening is not cost-effective in men at low or intermediate risk of prostate cancer but might be cost-effective in high-risk men.

Rather than examine screening outcomes, Robert Abouassaly, MD, of University Hospitals Case Medical Center in Cleveland, and colleagues sought to study the potential impact of the controversy on physician use of PSA screening tests. They searched records of their own institution and affiliated hospitals and identified all PSA tests ordered from Jan. 1, 2008, through Dec. 31, 2012. The search showed that 137,927 PSA tests were ordered over the five years, 43,498 for screening purposes.

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HIGH-INTENSITY FOCUSED ULTRASOUND AS SALVAGE THERAPY FOR PATIENTS WITH RECURRENT PROSTATE CANCER AFTER RADIOTHERAPY

Song W, Jung US, Suh YS

Korean J Urol 2014; 55: 91–96.

Purpose: To evaluate the oncologic outcomes and postoperative complications of high-intensity focused ultrasound (HIFU) as a salvage therapy after external-beam radiotherapy (EBRT) failure in patients with prostate cancer.

Materials and Methods: Between February 2002 and August 2010, we retrospectively reviewed the medical records of all patients who underwent salvage HIFU for transrectal ultrasound-guided, biopsy-proven locally recurred prostate cancer after EBRT failure (by ASTRO definition: prostate-specific antigen [PSA] failure after three consecutive PSA increases after a nadir, with the date of failure as the point halfway between the nadir date and the first increase or any increase great enough to provoke initiation of therapy). All patients underwent prostate magnetic resonance imaging and bone scintigraphy and had no evidence of distant metastasis. Biochemical recurrence (BCR) was defined according to the Stuttgart definition (PSA nadir plus 1.2 ng/mL).

Results: A total of 13 patients with a median age of 68 years (range, 60-76 years) were included. The median pre-EBRT PSA was 21.12 ng/mL, the pre-HIFU PSA was 4.63 ng/mL, and the period of salvage HIFU after EBRT was 32.7 months. The median follow-up after salvage HIFU was 44.5 months. The overall BCR-free rate was 53.8 percent. In the univariate analysis, predictive factors for BCR after salvage HIFU were higher pre-EBRT PSA ($p=0.037$), pre-HIFU PSA ($p=0.015$), and short time to nadir ($p=0.036$). In the multivariate analysis, there were no significant predictive factors for BCR. The complication rate requiring intervention was 38.5 percent.

Conclusions: Salvage HIFU for prostate cancer provides effective oncologic outcomes for local recurrence after EBRT failure. However, salvage HIFU had a relatively high rate of complications.

POPULATION-BASED COMPARATIVE EFFECTIVENESS OF SALVAGE RADICAL PROSTA- TECTOMY VS CRYOTHERAPY

Friedlander DF, Gu X, Prasad SM, et al

Urology 2014; 83: 653–657

Objective: To characterize population-based practice patterns, disease-specific and overall mortality, and cost associated with salvage cryotherapy (SCT) vs salvage radical prostatectomy (SRP).

Methods: We retrospectively identified 440 men who failed primary radiation therapy and subsequently underwent SCT ($n = 341$, 77.5 percent) or SRP ($n = 99$, 22.5 percent) between 1992 and 2009 from Surveillance, Epidemiology, and End Results-Medicare linked data. Propensity score analyses were used to compare overall and prostate cancer-specific mortality and associated Medicare expenditures for SRP vs SCT.

Results: Men undergoing SCT were more likely to be white ($P < 0.001$), less likely to be high school graduates ($P = 0.008$), and experienced shorter median time from diagnosis to salvage therapy (44.1 vs 60.1, $P < 0.001$) and from primary radiotherapy to salvage therapy (38.7 vs 55.8 months, $P < 0.001$). In adjusted analyses, overall mortality was higher (21.6 vs 6.1 deaths/100 person years, $P < 0.001$) for SRP vs SCT. There was a trend for higher prostate cancer-specific death rates with SRP vs SCT (6.5 vs 1.4 deaths/100 person years, $P = 0.061$). Medicare expenditures for SRP vs SCT were more than 2-fold higher (\$19,543 vs \$8,088, $P < 0.001$).

Conclusion: SRP vs SCT is associated with higher overall mortality and greater health care expenditures. However, longer follow-up is needed to assess long-term functional outcomes and cancer control.

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CHAPTER NEWS!

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NEW NCCN GUIDELINE SEEKS ‘MIDDLE GROUND’ ON PSA TESTING *(Continued from page 1)*

issued by the American College of Physicians, the American Cancer Society, and American Urology Association [AUA],” said Richard Hoffman, MD, professor of internal medicine at the University of New Mexico in Albuquerque.

For example, the most recent guidance from the AUA calls for routine PSA testing in healthy men, but only for those 55 to 69 years of age. The NCCN guidance obviously conflicts with the US Preventive Services Task Force (USPTF) recommendation against PSA testing in healthy men, Dr. Hoffman noted. That organization said the potential harms outweigh the benefits.

Still, the updated NCCN guidelines are an improvement from the old NCCN recommendations. “The new version is designed to be more evidence-based and to reduce testing and overdiagnosis,” he said in an email.

Both Dr. Carroll and Dr. Vickers emphasized that the key to the usefulness of the updated guidance is that it is linked to the NCCN prostate cancer treatment guidelines. “This should translate into less overtreatment,” they said.

“The NCCN has famously recommended the use of active surveillance instead of definitive treatment in early-stage low-risk disease. Half of all PSA-detected prostate cancers are low-risk disease,” Dr. Vickers explained.

Overall, the updated guidance seeks to “maximize the benefit and minimize the harm” of PSA testing, he said. Nevertheless, Dr. Hoffman, as an internist, has a pointed complaint about the NCCN recommendation to use PSA testing in age groups that have not been evaluated in randomized controlled trials.

The “best evidence supports the use of serum PSA for the early detection of prostate cancer,” according to the discussion section of the updated NCCN guidelines on the early detection of prostate cancer. However, the specifics of when, who, and how often to perform PSA testing “remain major topics of debate,” the report reads.

So how did the NCCN decide on age 45, which is an apparently novel age at which to start testing? The decision was not made on the basis of evidence from

the recent randomized trials conducted in Europe, which found a mortality benefit with screening but focused primarily on men 55 to 69 years of age.

Instead, the recommendation comes from observational data that suggest baseline PSA testing of men in their 40s and early 50s might allow for future prostate cancer risk stratification. Some of these data come from a large study of Swedish men in which a single PSA test before age 50 predicted subsequent prostate cancer risk up to 30 years later, as reported by Medscape Medical News.

“This suggests that one could perform early baseline testing and then determine the frequency of testing based on risk,” reads the updated NCCN guidance. In the words of Dr. Carroll, “a baseline PSA trumps family history or ethnicity as a [prostate cancer] risk factor.”

Indeed, the updated guideline calls for informed testing starting at age 45, with annual to biannual testing in those with a PSA above the age-specific median. For those below the median, a retest at age 50 is recommended. The median PSA levels are 0.7 ng/mL for men 40 to 49 years of age and 0.9 ng/mL for men 50 to 59 years. Annual or biannual follow-up is recommended for all men with a PSA value above 1.0 ng/mL.

Dr. Hoffman does not agree with this strategy. “The suggestion to start discussions about a baseline PSA test in men 45 to 49 years is troubling,” he said. “We have no evidence that closely following men with an elevated PSA level will ultimately reduce prostate cancer mortality,” he explained. “Testing younger men could lead to more false-positive results and unnecessary biopsies,” Dr. Hoffman pointed out.

Also, he noted, it is not known whether treating a cancer diagnosed at age 50 results in worse outcomes than treating a cancer diagnosed at age 45. “However, we do know that the younger men will have that much longer to live with treatment complications and the psychological burdens of a cancer diagnosis.”

Identifying the ideal age at which to discontinue testing is even more elusive than determining the start age, according to the NCCN panel. The panel members

uniformly agreed that PSA testing should only be offered to men with a life expectancy of more than 10 years. However, the stop date was not a unanimous decision. Therefore, the NCCN offers clinicians a set of cut-offs. Clinicians can discontinue screening at age 69; continue screening up to age 74 but increase the PSA threshold for biopsy in men 70 to 74 years; or discontinue screening at 75 years for men who have a PSA below 3.0 ng/mL.

Again, Dr. Hoffman has concerns about this guidance. “The updated version is also in contrast with other guidelines, including the AUA, which have backed off from recommending screening for men over the age of 70,” he said.

The updated NCCN guideline also states that men should generally be referred for a prostate tissue biopsy when their PSA exceeds 3 ng/mL. “This creates problems,” said Dr. Hoffman. “PSA increases with age, and using this low threshold will increase the number of false-positive tests and subject men to the harms of biopsy, which are now recognized to include a substantial risk for serious infections.

“The AUA suggests a biopsy threshold of 10 ng/mL to reduce these risks,” he added.

Presented at the 19th Annual NCCN Conference, 14 March 2014

Medscape Medical News, 19 March 2014



RELATIVE VALUE OF RACE, FAMILY HISTORY AND PROSTATE-SPECIFIC ANTIGEN AS INDICATIONS FOR EARLY INITIATION OF PROSTATE CANCER SCREENING

Vertosick EA, Poon BY, Vickers AJ

J Urol 3 April 2014, Epub

Introduction: Many guidelines suggest earlier screening for prostate cancer for high-risk men, defined in terms of race and family history. Recent evidence has suggested that a baseline prostate-specific antigen (PSA) level is strongly predictive of long-term risk of aggressive prostate cancer. We compared the utility of risk-stratifying early screening by race, family history and PSA at age 45.

Methods: Using estimates from the literature we calculated the proportion of men targeted for early screening using either family history, African-American race or PSA as the criterion for high risk. We calculated the proportion of prostate cancer deaths that would occur in those men by age 75.

Results: Screening based on family history would involve 10 percent of men accounting for 14 percent prostate cancer deaths. Using African-American race as a risk criterion would involve 13 percent of men accounting for 28 percent deaths. In comparison, 44 percent of prostate cancer deaths occur in the 10 percent of men with the highest PSA levels at age 45. In no sensitivity analysis for race and family history did the ratio of risk group size to number of prostate cancer deaths in that risk group approach that of PSA.

Discussion: Basing decisions for early screening on PSA at age 45 gave the best ratio between men screened and potential cancer deaths avoided. Given the lack of evidence that race or family history affects the relationship between PSA and risk, PSA-based risk stratification would likely include any African-Americans or those with a family history destined to experience aggressive disease. Differential screening based on risk should be informed by baseline PSA.

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

"Step right up and let me predict your vitamin D level without a blood test?"

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

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

Bottom Line:

A new study suggests that vitamin D blood levels before prostate cancer surgery were NOT associated with an increased risk of aggressive prostate cancer. And, other studies now suggest that predicting your vitamin D blood level based on your lifestyle is fairly accurate so many folks may not need a blood test in the future. Step right up! Moyad is going to guess your vitamin D level based on your overall health, weight, exercise level, and diet and I will only charge you a case of beer for my services!

Columbia University urologic researchers published a wonderful little study on 100 consecutive men with a vitamin D blood test about to have a radical prostatectomy.¹ They essentially found no correlation with higher or lower vitamin D blood levels and adverse or poor pathology after surgery (one-third of their patients were deficient). So, this study preliminarily suggests that vitamin D might have no impact on prostate cancer. But the authors acknowledge that there has been so much mixed information that it is tough to predict if vitamin D will really end up having an impact on cancer. (I am not optimistic.)

Simultaneously, there have been studies showing the strong correlation between lifestyle changes and higher vitamin D blood levels.^{2,3} For example, the amount of time you spend outdoors, greater physical activity, and the more you consume foods/supplements (like a multi-vitamin) with vitamin D the greater the chance of having a higher vitamin D blood level. However, individuals with higher BMI (greater weight/waist size), elderly, and those in poor health were more likely to have low blood levels of vitamin D. The problem with vitamin D right now is the test is being ordered more than ever before but the research on the benefits of vitamin D for overall health (except bone health) is getting weaker/more controversial than ever before. For example, in one of the best

trials for weight loss over 12 months it did not work better than placebo in women. (Male studies have been similar.)⁴ The biggest concern I have had about vitamin D over the years is there has been so much emphasis on taking large amounts of this supplement to improve overall health rather than educating folks on the fact that as individuals become healthier, their vitamin D level naturally begins to increase. In other words, it is not the vitamin D that makes you healthy but healthy people make vitamin D look good.

So, instead of an obsession with taking mega-doses of vitamin D it should be an indicator to work on lifestyle changes to lose weight and exercise more. And, if this does not increase your vitamin D blood level then taking the supplement in higher dosages may make more sense. Regardless, I do believe in a few years I will be able to guess your vitamin D blood level with good accuracy after you fill out a questionnaire.

Wow! Think about it! I could travel with the circus or carnivals all over and yell "Step right up and let me guess your vitamin D level." But before that you have to step on a scale so I know your true weight and waist size (okay, this is cheating but I think you get my point). Anyhow, after I guess your vitamin D blood level and it is confirmed by your doctor that it is indeed accurate, you have to donate to my beer fund. And, the good news is that moderate alcohol intake has been associated with a higher vitamin D blood level in some studies!⁵ So, this is a win-win situation; I save you money on future blood tests and you give me beer instead of money!

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COMBINATION AND SEQUENCING: THE FUTURE OF CANCER IMMUNOTHERAPY IN PROSTATE CANCER

By Alex Franzusoff, PhD, SVP Research & Development, Bavarian Nordic

Until a few years ago, the only treatment shown to improve overall survival (OS) for prostate cancer patients was chemotherapy. Since 2010, patients now have a number of FDA approved options including targeted therapies such as abiraterone (Zytiga®) and enzalutamide (Xtandi®), the radiotherapy Radium-223 (Xofigo®) and the first approved immunotherapy, sipuleucel-T (Provenge®). Additionally, promising investigational therapies are being developed, such as PROSTVAC®, a cancer immunotherapy which showed an 8.5 month improvement in median overall survival versus the control group in a randomized, placebo controlled Phase 2 study. A global Phase 3 trial is currently underway.

While these new therapies represent a significant improvement in treatment options for prostate cancer patients, it is becoming clear that their true potential will depend on how successfully we can combine these treatments to maximize their therapeutic benefits. Cancer immunotherapy is expected to serve as the foundation for future combination therapeutics because they've historically shown low levels of toxicity due to their unique mechanisms of action.

So... *What is Cancer Immunotherapy?*

Our body's own immune system is actually a very capable defense system, constantly protecting us from threats like bacteria, viruses and even cancer. However, while our immune system can effectively target and kill most invaders to the body, especially if the immune system is pre-trained with preventive vaccines, malignant cancer cells are often ignored by the immune system and begin to grow unchecked. The ability of cancer cells to evade the immune system is what makes cancer so difficult to treat. But what if we could teach the body to recognize these cancer cells and fight them off?

The term "cancer immunotherapy" encompasses treatments designed to help the body's immune system to identify and attack these cancerous cells. Because immunotherapies aim to trigger an immune response to tumor cells, rather than directly attacking the cancer, they

have been associated with milder side-effects than traditional chemotherapy and hormone treatments. It should also be noted however, that time and repeated dosing are needed before the immunotherapy can successfully train the immune system to recognize and begin eliminating cancer cells. Recently, interest in the cancer immunotherapies has grown tremendously, particularly in anticipation of their potential in combination, either with other immunotherapies or anti-androgen therapies and radiotherapy. By attacking the cancer from multiple angles, oncologists believe that we could see significantly improved treatment outcomes, and revolutionize how we treat prostate cancer and other cancers.

How will these treatments be combined?

In chemotherapy, we basically blast large amounts of cyto-(or cell) toxic therapy at cancer cells, hoping to kill them. Consider this the "shotgun" approach to treatment. While chemotherapy has been effective in killing cancer cells, significant damage is also done to the healthy cells in the body and hinders the immune system following treatment. This is the main reason why chemotherapy is often associated with severe side effects.

However, by using anti-androgen therapies or radiotherapy together with cancer immunotherapies, we can be much more targeted in our attack on cancer cells. These could be considered the "rifle" or, in the more modern medical context, "laser" approaches. Using this technique, we may be able to slow down cancer growth, thus giving the immune system time to identify and eliminate the cancer. Giving the immune system this time to train and develop its defenses against cancer cells will also allow it to protect the body against future recurrences. Combination therapy is focused on how we can successfully pair these "laser" treatments together to maximize their benefits. In theory, these therapies could be synergistic, with the added benefit that they could potentially be given in lower doses when combined, resulting in even fewer side effects for patients. Much work still needs to be done, how-

ever, as we continue to look for the most effective and safe combinations. Furthermore, there are still questions to address regarding simultaneous versus sequential treatment, low dose versus high dose, and not inconsequentially, the potential cost to patients and payers for receiving combination therapies.

Simultaneous vs. Sequenced Therapy

It is important to understand that cancer evolution and progression are the keys to developing a proper treatment plan. The plan of attack to treat prostate cancer may be highly dependent on the stage of disease progression, and therefore the choice between simultaneous or sequenced treatment combinations is highly dependent on the stage of the cancer at the start of treatment. If caught at an early enough stage, a physician may have the opportunity to halt or slow the disease through a series of treatments to help eliminate it.

Because the immune system needs time to mount an immune response to the tumor cells, it is believed that immunotherapy treatment would provide the most benefit when given early on in treatment. Theoretically, it would make sense to treat a patient with an immunotherapy first, to "prime" the immune system against known tumor antigens, such as PSA expressing cells. This could be followed by treatment with anti-androgen therapy and/or radiotherapy to break-up the tumor or at least slow its growth. This could deliver a "one-two punch" to the tumor, first from the im-

(Continued on page 8)



PRIMARY ADT OF NO BENEFIT*(Continued from page 1)*

higher baseline PSA values, were more likely to have Gleason grade ≥ 7 , more likely to have stage $\geq T2b$ disease at diagnosis, and more likely to meet AUA criteria for intermediate or high-risk disease (versus low-risk).

The data showed that 49 percent of the ADT group died during follow-up versus 28 percent of the no-ADT group. After adjustment for imbalances in baseline characteristics, the mortality difference did not achieve statistical significance. A propensity-matched analysis also showed no difference in survival between the ADT and no-ADT groups.

Similarly, prostate cancer-specific mortality (13 percent versus 5 percent) did not differ significantly in a conventionally adjusted analysis (HR 1.03) or propensity-matched analysis (HR 1.01). The ADT group also had a nonsignificant higher mortality associated with other cancers and cardiovascular disease.

“Our main conclusion is that primary ADT does not seem to be an effective strategy as an alternative to no therapy among men diagnosed with clinically localized prostate cancer who are not receiving curative-intent therapy,” the authors noted. “The risks of serious adverse events and the high costs associated with its use mitigate against any clinical or policy rationale for primary ADT use in these men.”

The analysis counters most of the assumptions that have formed the basis for use of primary ADT, according to Charles J. Ryan, MD, of the University of California San Francisco.

“There has been a historical assumption that use of primary ADT would be something that would control the cancer in men who don’t want RP or RT,” stated Ryan, a spokesperson for the American Society of Clinical Oncology. “I think, in many cases, it [primary ADT] was done without a lot of thought.

“I don’t think this will impact somebody’s decision to do active surveillance,” he added. “I think it should impact clinicians’ decision to use hormonal therapy in lieu of local therapy in men who do choose active surveillance.”

MedPage Today, 17 March 2014

PSA SCREENING TESTS DOWN*(Continued from page 1)*

To evaluate the possibility of a generalized trend in use of screening tests, the authors evaluated 250,602 cholesterol tests ordered for men during the same time period.

From January 2008 to March 2009, the frequency of testing increased significantly ($P < 0.001$), consistent with patterns dating back to the widespread adoption of PSA testing in the 1990s. Following publication of U.S. and European clinical trial results in 2009, use of PSA screening tests decreased significantly until May 2012, when the USPSTF recommended against routine screening ($P < 0.001$).

Publication of the screening-trial results was associated with a significant decrease in orders for screening PSA tests at urban/academic centers ($P < 0.05$) but not at suburban or rural hospitals. Following the USPSTF decision in 2012, orders for screening PSA tests decreased significantly at rural hospitals ($P < 0.001$). Requests for screening tests decreased at suburban facilities but not significantly so.

Internists accounted for 64.9 percent of all tests ordered during the 5-year period, followed by family physicians (23.7 percent), urologists (6.1 percent), and oncologists (1.3 percent). Test orders declined across the board after publication of the trial results and accelerated following the USPSTF announcement, except among family physicians. The largest decrease occurred among urologists.

Despite finding evidence of a significant decline in orders for PSA screening tests, the authors offered a cautious interpretation.

“Overall, we believe that although we detected a statistically significant decrease in PSA use with time, the absolute decrease was small and the clinical significance of our findings is uncertain,” Abouassaly and colleagues concluded. “Further study is needed to determine the long-term effects of these recommendations on the screening, diagnosis, treatment, and prognosis of this prevalent malignancy.”

MedPage Today, 18 March 2014

BIOMARKER FOR RESISTANCE TO ENZALUTAMIDE IN PROSTATE CANCER

A new biomarker may help predict resistance to enzalutamide (Xtandi®) in men with prostate cancer, according to data presented at the American Association for Cancer Research (AACR).

“The biomarker is androgen-receptor splice variant-7 (AR-V7), a truncated form of the androgen-receptor protein that lacks the ligand-binding domain targeted by Xtandi but remains constitutively active as a transcription factor,” explained Emmanuel Antonarakis, MD, assistant professor of oncology at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center in Baltimore.

Researchers used quantitative RT-PCR to test circulating tumor cells (CTCs) for the presence or absence of AR-V7 in 31 men with metastatic castration-resistant prostate cancer (mCRPC) beginning Xtandi. Of the 31 men, 12 (38.7 percent) had detectable AR-V7 mRNA in their CTCs. PSA response rates were worse in men testing AR-V7-positive than in those testing negative (0.0 percent vs 52.6 percent; $P = 0.004$).

Median PSA progression-free survival (PFS) was shorter in men testing positive for AR-V7 than those testing negative (1.4 vs 5.9 mo; hazard ratio [HR], 7.4; log rank $P < 0.001$), as was median PFS (2.1 vs 6.1 mo; HR; 8.5; $P < 0.001$).

On a multivariable Cox regression analysis, the presence of AR-V7 (HR, 3.5; $P = 0.027$), baseline PSA (HR, 1.01; $P = 0.042$), and prior response to abiraterone (HR, 5.4; $P = 0.039$) were all independently predictive of PSA PFS. Researchers also found that AR-V7 (HR, 3.7; $P = 0.026$) and prior abiraterone use (HR, 8.7; $P = 0.049$) were both independently predictive of PFS.

Even though results are early, “we believe these data have immediate clinical implications,” Dr. Antonarakis said. “We suggest that patients with detectable AR-V7 in their CTCs be steered away from these AR targeting therapies, such as enzalutamide, and instead be offered options such as chemotherapy or radiation,” he told attendees.

(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 is not necessarily those of Us TOO International.

a1p1c1 The problem about what to do about screening recommendations never seems to go away. The latest comes from the NCCN and is presented as a “middle ground.” One can't help but wonder what part of their suggestion qualifies as middle. They make a recommendation not advocated either by the American Cancer Society or the U.S. Public Health Services Task Force (USPTF). Once again, the only study finding a benefit to screening started testing most men at age 55. Not one study has ever demonstrated a benefit from testing men starting at age 45. The authors say it is more evidence-based than their previous recommendation. Unfortunately, without any evidence for a reduction in mortality by testing at this early age, they are potentially subjecting many men to both unnecessary testing and treatment. Their recommended actions based on the initial PSA level is also not based on any mortality data. They also recommend that men have a biopsy if their PSA is above 3 ng/mL without discussing PSA velocity at all. This too, will result in many men getting unneeded biopsies. As for the age to stop screening, their criteria vary but again they are not consistent with the evidence-based guidelines of the USPSTF or American Cancer Society.

The Bottom Line: The NCCN guidelines for testing men beginning at age 45 are not supported by any evidence for a reduction in cancer mortality; and before getting tested men should be made aware of this shortcoming.

a2p1c2 Is androgen deprivation therapy (ADT) helpful in men with localized prostate cancer? This important question has never been tested in a properly designed study. Now, a study by Potosky and co-workers suggests that ADT is NOT effective for localized disease, meaning it does not reduce prostate cancer mortality. Unfortunately, the study is retrospective and uncontrolled. As happens in most uncontrolled trials, the study groups were not balanced. As the authors stated, the men receiving ADT were older, had a higher PSA, were more likely to have grade 7 or higher, have

stage T2b or higher, and were less likely low risk. With so many differences, any findings from this study are suspect. There is simply no way to draw any conclusions about ADT from this study.

The Bottom Line: A study suggesting that ADT was not an effective treatment for localized disease does not provide reliable information and therefore this study is not useful for assessing the value of this treatment in this patient group

a3p1c3 Given the changing recommendations for screening, the question is whether doctors are changing their practice of routinely ordering a PSA test. The study by Abouassaly et al suggests that PSA testing has been declining over the past several years, at least in Cleveland. Whether this has occurred nationally is unclear at this time.

The Bottom Line: Despite the recommendations by the USPSTF, many doctors and men are still choosing to be tested believing that getting tested does not require treatment to occur if cancer is found. An important question for health care regulators is whether the money being spent to perform these tests and follow-up care could be better utilized.

a4,5;p2;c2,3 Men with residual cancer following RT have a number of treatment options, including salvage cryotherapy, RP and High Intensity Focused Ultrasound (HIFU). Is one better than the other? Friedlander and co-workers conducted a retrospective analysis using SEER-Medicare linked data to compare salvage RP and salvage cryotherapy, and Song et al conducted a small, retrospective study on men undergoing HIFU. In the first study, better outcomes and lower costs occurred with salvage cryotherapy compared to RP. However, as has often been written in this column, the validity of these findings is unclear due to the retrospective design and results could simply be due to different characteristics of the two groups. For example, there was an unequal proportion of men who had brachytherapy, brachytherapy + external beam RT, and pre-treatment ADT. The study of HIFU only included

a heterogeneous cohort of 13 men and follow-up is too short. The only way to determine the relative benefits of these three salvage therapies is by conducting a prospective, randomized trial using survival as the primary outcome.

The Bottom Line: Neither study provides useful data for determining the relative merits of any of these salvage therapies in men failing RT.

a6p4c1 Considerable effort is being directed toward risk assessment to identify the best men for prostate cancer screening. Obtaining a baseline PSA starting at age 45 combined with family history and race are the three factors being used. The study by Vertosick et al attempts to determine the proportion of cancer deaths associated with each of these factors and they found that PSA level at age 45 was the most important factor. That may explain, in part, why some groups such as NCCN are recommending this be done in all men. Two problems must be addressed with this approach. First, as stated earlier, no data has yet demonstrated that screening men at age 45 will result in a significant drop in mortality in those men. The fundamental issue is whether a high percentage of those men have an aggressive cancer that already has microscopic spread by that time. The recent findings from the Scandinavian trial of WW vs. RP provide support for this concern because surgery did not alter prostate cancer mortality in high risk men.

The Bottom Line: The PSA test may be inadequate for finding the bad cancers early enough to make a difference in many of the men at risk for dying from this disease. Better markers are needed.



ENZALUTAMIDE BIOMARKER

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However, at least one expert feels that it is too soon to steer patients who may have detectable AR-V7 in their CTCs away from Xtandi. "Before we deprive a man of an effective therapy, we really need more data on this," said M. Dror Michaelson, MD, PhD, clinical director of the Genitourinary Cancer Center at Massachusetts General Hospital in Boston.

"For one thing, there are many different technologies that are used to extract CTCs. There are no standards yet, and the technology is not available or accessible to everyone at this time," he said.

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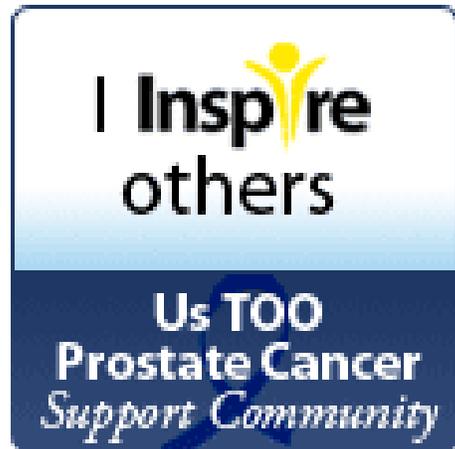
COMBINATION AND SEQUENCING *(Continued from page 5)*

mune system, which has had an opportunity to mount an immune response to the cancer cells, and then with a complementary therapy that delivers its blow from a different direction.

However there may come a point where it is too late to treat prostate cancer with sequencing. Patients suffering from late stage prostate cancer may not have time to be treated in a stepwise fashion, so physicians may need to access all the artillery at once to launch a full-on attack of the cancer. Fortunately, our experience has evolved to understand that simultaneous combinations do work together well. Therefore, cancer immunotherapy can be applied in combination simultaneously with some other therapies with the promise of accelerated therapeutic benefit in those patients with more advanced disease.

While we have just started to scratch the surface of combination therapy, we are beginning to realize the potential to change lives of cancer patients, particularly those with prostate cancer. As we continue to develop new treatments and

potential combinations, it will be especially exciting to see how these treatments complement one another, and hopefully are successful enough to replace traditional chemotherapy and other toxic therapies as treatment options.



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