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Affected by Prostate Cancer?



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Hot SHEET

Us TOO INTERNATIONAL Prostate Cancer Education and Support Network

Prostate Cancer Metastasis Risk Higher in Some AS Patients

Metastases develop in a small proportion of men placed on active surveillance (AS) for prostate cancer (PCa), but the risk is significantly higher in some men than others, such as those with Gleason 7 tumors, reported a new study published in *The Journal of Urology* (Vol. 195, pp. 1409-1414, 2016).

In a study of 980 men placed on AS – 769 with low-risk and 211 with intermediate-risk PCa – a team led by Laurence Klotz, MD, of Sunnybrook

Health Sciences Centre in Toronto found that 30 men (3%) progressed to metastatic disease at a median of 6.3 years after diagnosis. Metastases developed in 13 (10%) of 133 patients with Gleason 7 disease.

Metastases occurred in 16 low-risk and 14 intermediate-risk patients, and developed in bone in 18 patients and lymph nodes in 13. Of the 30 men, 15 died from PCa, four died of other causes, and 11 are alive with metastases. Men with intermediate-risk disease were at higher risk for metastasis, but those with Gleason score 6 and PSA

levels greater than 10 ng/mL were not at increased risk.

In multivariate analysis, a PSA doubling time less than three years vs. greater than three years was associated with a 3.7-fold increased risk of metastasis. Gleason score 7 compared with 6 was associated with a three-fold increased risk. The presence of three or more positive biopsy cores was associated with a 2.7-fold increased risk compared with fewer positive cores.

The authors concluded that AS appears safe in men at low-risk and in select men at

(Continued on page 4)

USPSTF Re-evaluates PSA Testing

The US Preventive Services Task Force (USPSTF) is updating its controversial guidance about prostate cancer screening, and a final research plan was published online last week.

The plan will guide a systematic review of the available evidence on prostate cancer screening. In turn, the systematic review “will form the basis of the Task Force’s updated recommendation statement on this topic,” according to the USPSTF website.

In 2012, the organization formally recommended against routine PSA-based prostate cancer screening for healthy men, regardless of age. However, the document left room for use of the test in the clinic. “Clinicians should understand the evidence but individualize decision-making to the specific patient or situation,” read the final document, which was published in *Annals of Internal Medicine* (Vol. 157, pp. 120-134, 2012). Nonetheless, recent reports indicate that the use of the PSA test has dropped, especially among primary care providers.

In their research plan, the USPSTF will be looking at multiple “key questions.” The very first question addresses higher-risk men: “Does the effectiveness of PSA-based screening vary by subpopulation/risk factor (e.g., age, race/ethnicity, family history, and clinical risk assessment)?”

“But the question might not be fully answerable,” said Richard Hoffman, MD, MPH, an internist at the University of Iowa, and an expert in shared decision-making about prostate cancer screening. “Finding high-quality data to answer this will be challenging,” he told *Medscape Medical News*. None of the major

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Timing of Androgen Deprivation Therapy in Patients with Prostate Cancer with a Rising PSA (TROG 03.06 and VCOG PR 01-03 [TOAD]): A Randomised, Multicentre, Non-Blinded, Phase 3 Trial

Duchesne GM, Woo HH, Bassett JK, et al
The Lancet Oncology 4 May 2016; Epub

Androgen deprivation therapy (ADT) is offered to men with prostate cancer who have a rising PSA after curative therapy (PSA relapse [PSAR]) or who are considered not suitable for curative treatment; however, the optimal timing for its introduction is uncertain. We aimed to assess whether immediate ADT improves overall survival (OS) compared with delayed therapy.

In this randomised, multicentre, phase 3, non-blinded trial, we recruited men through 29 oncology centres in Australia, New Zealand,

and Canada. Men with prostate cancer were eligible if they had PSAR after previous attempted curative therapy (radiotherapy [RT] or surgery, with or without postoperative RT) or if they were not considered suitable for curative treatment (because of age, comorbidity, or locally advanced disease). We used a database-embedded, dynamically balanced, randomisation algorithm, coordinated by the Cancer Council Victoria, to randomly assign participants (1:1) to immediate ADT (immediate *(Continued on page 4)*

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Bevacizumab Plus ADT May Up Survival in Recurrent Prostate Cancer

Adding bevacizumab to androgen deprivation therapy (ADT) resulted in improved relapse-free survival (RFS) in men with hormone-sensitive prostate cancer, according to a study published online in the *Journal of Clinical Oncology* on 4 April 2016.

ADT is a typical treatment strategy for men with recurrent prostate cancer who have received local therapy. Researchers sought to investigate efficacy and toxicity of short-course ADT with or without bevacizumab, a vascular endothelial growth factor A (VEGF-A) inhibitor, in men with hormone-sensitive prostate cancer.

For the phase 2 study, researchers enrolled 102 men who had an increasing PSA no greater than 50 ng/mL and a PSA level that had doubled in less than 18 months. Patients were eligible if they were free of metastases or had low-burden, asymptomatic metastases.

Participants were randomly

assigned 2:1 to receive ADT (as bicalutamide) plus bevacizumab or ADT alone for six months.

Results showed that patients receiving ADT plus bevacizumab had a biochemical relapse-free survival of 13.3 months compared with 10.2 months for ADT alone (HR, 0.47; 95% CI, 0.29–0.77; P = 0.002). For postprostatectomy patients, relapse was defined as a rise in PSA above 0.2 ng/mL. For primary radiation therapy patients, relapse was defined as rise in PSA above 2.0 ng/mL.

In terms of safety, 36% of patients who received ADT plus bevacizumab developed hypertension.

Although these findings are encouraging, long-term follow-up is necessary to determine whether some patients achieve a durable PSA response and are able to discontinue ADT for prolonged periods.

Renal & Urology News
8 April 2016

Active Surveillance Is Often 'Not'

Only one in three men with low-risk prostate cancer receive appropriate follow-up when assigned to active surveillance (AS) of their disease, a new study suggests. Findings add to a growing body of evidence suggesting that prostate cancer risk may be higher than expected in men categorized as having low-risk disease.

Under AS, both patients and providers “may have a tendency to get a little lackadaisical,” stated study investigator Gregory Auffenberg, MD, from the University of Michigan, in Ann Arbor. The result may be a “potentially higher risk than what we all agreed on — and what patients

thought they were getting into — when we embarked on the surveillance pathway.”

The findings, presented at the American Urological Association (AUA) 2016 Annual meeting, point to biopsies as the main missing link. “Biopsies are not comfortable, they’re not risk-free, and patients don’t like them,” he said.

But it is likely that provider factors also contribute to suboptimal AS. “Guidelines for AS are not crystal clear, but a conservative estimate is that men should undergo PSA testing roughly every six months and should undergo a repeat biopsy every two years,” said Dr. Auffenberg.

Medicare Suspends Penalty for PSA Testing Proposal

The Centers for Medicare & Medicaid Services (CMS) has “temporarily suspended development” of a proposal that would have penalized physicians for performing “non-recommended” prostate cancer screening with the PSA test, the agency said in March 2016. However, the idea of Medicare establishing parameters for PSA testing has not been completely abandoned.

In an online statement, CMS said it will continue to solicit input “to determine whether a restructured, appropriate-use PSA measure should be developed.” The appropriate use of PSA testing is being investigated to “address overuse and patient safety,” according to CMS.

The announcement has been expected since early March, when a key advisory group to Medicare intended to recommend that CMS not consider further recommendation of the PSA penalty idea.

(Continued on page 5)

To assess compliance with this, his study analyzed AS in 431 men with low-risk prostate cancer who were followed for at least two years. The men from the Michigan Urological Surgery Improvement Collaborative database were followed by 232 Michigan urologists from 42 practices. The median age of the men was 66 years, and the median baseline PSA level was 5.3 ng/mL. Seventy-five percent of the men had a biopsy Gleason score of ≤6, and 17% had Gleason 3+4 disease.

Between January 2012 and September 2013, fewer than

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Doc Moyad's What Works & What is Worthless Column, Also Known As "No Bogus Science" Column

Depression Rx pills not working well enough; then why not add a dietary supplement, says Harvard

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.

Bottom Line:

New and old research suggests an increased risk of depression in some cancer patients; and there is now an emphasis to increase awareness of this issue (aka use a multidisciplinary approach). Okay great, then why not mention some dietary supplements from the new Harvard group analysis on tough to treat depression????????? (Note the many question marks because I am perplexed this was not published long, long ago).¹

I was recently inundated by some media folks who thought it was remarkable that a fairly prestigious Harvard Medical School and Australian group published in a major psychiatry medical journal the conclusion that some dietary supplements such as SAM-e, omega-3 fatty acids, and/or L-methylfolate and others could help patients with tough-to-treat depression IN ADDITION TO THEIR prescription medications, and they wanted my

comment on this study. Why me, you ask? Well, because last year I wrote in the best-selling book, "The Supplement Handbook" (by Moyad, shameless plug, of course, why not? I like to have money for beer) about an almost identical conclusion. I had to tell these reporters that this was not an original study from Harvard doctors but a summary of 40 PAST STUDIES on dietary supplements identical to the ones I analyzed for the book. Ergo, this has been known for years but simply because some Harvard faculty published a summary of this data in the *American Journal of Psychiatry* there was some verve and joy! And, these authors did a beautiful thing but what they really did was help to validate that depression as well as many diseases today need multiple approaches for potential success. The tragedy is that this and other articles should have been published five to 10 years ago.

Now, I am not saying that these supplements definitely

can help with depression but I am saying that numerous conventional and alternative options with a good safety record exist out there where the benefit exceeds the risk, in some cases, when trying them with your doctor monitoring you. But the only reason they are not being used is arguably due to a lack of awareness or education in this area and the inability to admit that often the one-size-fits-all approach does not work for all. Depression itself, whether it is caused by a cancer diagnosis or treatment, or made worse by cancer itself, needs as much attention as any other side effect we like to talk about with prostate cancer.^{2,3}

Because without optimal mental health, one cannot easily attain optimal physical health and vice versa. So, prescriptions, exercise, therapy/counseling, rTMS = repetitive Transcranial Magnetic Stimulation (which I will discuss in a future column), and a variety of other methods can help, including some die-

tary supplements (aka "drugs" when they work, but let's just call them supplements to play by the rules). I find it interesting that the compound SAM-e, for example, mentioned by the Harvard group is actually a prescription drug in many countries except in the US where it is a dietary supplement. Regardless, thank you Harvard and Australia for reminding all of us that we in conventional medicine do not always have the answers to complex diseases and a synergistic or multidisciplinary or open evidence-based approach could make a difference for so many struggling out there with depression.

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2. Lu D, Andersson TM, Falk K, et al. *JAMA Oncol* 28 April 2016; Epub.
3. Dinh KT, Reznor G, Muralidhar V, et al. *J Clin Oncol* 11 April 2016; Epub.

New FDA-Approved Prostate Tool: Will You HIFU?

Since the approval of two high-intensity focused ultrasound (HIFU) devices last fall by the US Food and Drug Administration (FDA), the field of urology in the US has been in limbo. The technology – used in Australia, Canada, and Europe for the treatment of prostate cancer – was not approved for that indication in the US because the device manufacturers were unable to demonstrate efficacy against the cancer. Instead, the approval of HIFU was simply for "prostate ablation," leaving a huge ques-

tion mark for clinicians, patients, and insurers. The FDA stopped short of telling clinicians how to practice medicine, saying "clinicians, in consultation with their patients, should decide how best to use this tool," explained FDA spokesperson and urologist Charles Viviano, MD, PhD, during a plenary session at the American Urological Association (AUA) 2016 Annual meeting. Has the FDA decision resulted in confusion? "Oh yeah," stated Michael Koch, MD, the plenary moderator and

professor and chair of the department of urology at Indiana University. "Is that a bad thing? Not at all," said Samir Taneja, MD, director of urologic oncology and the genitourinary oncology program at the NYU Cancer Institute in New York, who moderated a case panel discussion during the plenary. "I think it's a good thing. It's really critically important for our field to really rigorously study how it should be used." "Learn from Australia and Canada," cautioned Nathan Lawrentschuk, MBBS, plenary

speaker and associate professor of urology at the University of Melbourne who practiced in both countries, where the technology has been used for more than a decade. "Do not make the same mistakes we have for whole-gland prostate treatment with HIFU. In my opinion, it is a fringe treatment used in patients on the fringe of mainstream medicine," he said.

In stark contrast, the 15- to 20-year experience with HIFU in Europe has been a big

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USPSTF & PSA Testing *(Continued from page 1)*

screening trials enrolled men younger than 50 years, most subjects were white, and investigators did not routinely assess clinical risk.

“While some studies are now recruiting patients to address screening in higher-risk populations, it will likely take at least a decade to determine the effects of screening on morbidity and mortality,” he summarized. In the meantime, Dr. Hoffman is concerned that “abandoning PSA screening” is proving harmful. The rate of distant-stage prostate cancers in the US is increasing, according to a population-based study for which he was lead author (*Cancer Epidemiol Biomarkers Prev.*, Vol. 25, pp. 259–263, 2016). However, “it’s too early to tell whether this will lead to an increase in prostate cancer mortality,” he said.

The USPSTF research plan separates the review of evidence about the potential harms of PSA testing, biopsy, and treatment. “This separation is a good idea,” said Dr. Hoffman. “While the literature on biopsy harms is pretty comprehensive, we

still need to better understand the implications of overdiagnosis and overtreatment,” he pointed out.

Emerging evidence on the benefits and harms of active surveillance is an especially important area of research. “Many experts believe that the harms of screening can be mitigated by withholding active treatment for men whose cancers appear unlikely to ever cause clinical problems,” Dr. Hoffman explained.

Jesse D. Sammon, DO, a urologist from Brigham and Women’s Hospital in Boston believes that current recommendations from the American Cancer Society and the American Urological Association have evolved intelligently. Both organizations now recommend joint decision-making about PSA testing with men 55 to 69 years of age. “The great survival benefit [of the testing] is in this age group,” he stated.

“Therefore, the mortality benefit justifies consideration of the test, in spite of known risks,” Dr. Sammon argued.

Medscape Medical News
4 May 2016

PCa Metastases with AS *(Continued from page 1)*

intermediate-risk PCa, particularly those with Gleason score 6 and PSA levels greater than 10 ng/mL. The presence of Gleason pattern 4 on diagnostic biopsy was associated with a three- to four-fold increased risk of metastasis. Patients with Gleason pattern 4 should be offered AS with caution, according to the investigators.

In editorial comments accompanying the new report, Michael O. Koch, MD, of the Indiana University School of Medicine in Indianapolis said Dr. Klotz and his colleagues contribute to the growing body of knowledge of the

usefulness of AS for managing PCa, but observed: “While the authors have highlighted the risk factors for developing metastases in patients treated with AS, they may be overly optimistic about the safety of this management strategy, particularly in patients with Gleason 7 disease.”

He pointed out that the median follow-up was only 6.3 years, so the number of men with Gleason 7 disease in whom metastases will develop will grow even more.

Renal & Urology News
12 April 2016

Timing of ADT *(Continued from page 1)*

therapy arm) or to delayed ADT (delayed therapy arm) with a recommended interval of at least two years unless clinically contraindicated. Randomisation for participants with PSAR was stratified by type of previous therapy, relapse-free interval, and PSA doubling time; randomisation for those with non-curative disease was stratified by metastatic status; and randomisation in both groups was stratified by planned treatment schedule (continuous or intermittent) and treatment centre.

Clinicians could prescribe any form and schedule of ADT and group assignment was not masked. The primary outcome was OS in the intention-to-treat population. The trial closed to accrual in 2012 after review by the independent data monitoring committee, but data collection continued until February 26, 2014. It is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12606000301561) and ClinicalTrials.gov (NCT00110162).

Between Sept 3, 2004, and July 13, 2012, we recruited 293 men (261 with PSAR and 32 with non-curative disease). We randomly assigned 142 men to immediate ADT and 151 to delayed ADT. Median

follow-up was five years (IQR 3.3–6.2) from the date of randomisation. Sixteen (11%) men died in the immediate therapy arm and 30 (20%) died in the delayed therapy arm. Five-year OS was 86.4% (95% CI 78.5–91.5) in the delayed therapy arm versus 91.2% (84.2–95.2) in the immediate therapy arm (log-rank $p=0.047$). After Cox regression, the unadjusted HR for OS for immediate versus delayed ADT was 0.55 (95% CI 0.30–1.00; $p=0.050$). Twenty-three men had grade 3 treatment-related adverse events. One hundred five (36%) men had adverse events requiring hospital admission; none of these events were attributable to treatment or differed between treatment-timing groups. The most common serious adverse events were cardiovascular, which occurred in nine (6%) men in the delayed therapy arm and 13 (9%) in the immediate therapy arm.

Immediate ADT significantly improved OS compared with delayed intervention in men with PSA-relapsed or non-curative prostate cancer. Results provide benchmark evidence of survival rates and morbidity to discuss with men when considering their treatment options.

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PSA Testing Penalty

(Continued from page 2)

In the now-suspended proposal, non-recommended PSA testing was defined by the guidance from the US Preventive Services Task Force (USPSTF), and referred to routine use of the test to screen otherwise healthy men of all ages. Importantly, PSA testing for diagnostic or surveillance purposes was exempt from the proposal.

Earlier this month, two experts expressed satisfaction that the proposal was to be shelved. Stacy Loeb, MD, a urologist at New York University stated "I am very relieved to hear that this proposed policy was reversed. The proposal would have "not allowed patients to make informed choices about their own healthcare."

"I am certainly glad cooler heads prevailed," said Alexander Kutikov, MD, a urologic oncologist at the Fox Chase Cancer Center in Philadelphia. He called the proposal to penalize doctors for using the PSA test "rather Draconian."

In early March, the AUA issued a statement, saying that it "responded swiftly and strongly" to the proposal, organizing public review and comment on the measure.

"This is a perfect example of how strong we can be when we all work together and speak loudly with one voice," David F. Penson, MD, a urologist at Vanderbilt University in Nashville, who is chair of the AUA Public Policy Council, said in the statement. "Essentially, our galvanized response to these threats to PSA helped stop these measures from moving forward without input from urologists and patients."

Medscape Medical News
28 March 2016

Active Surveillance Is Often 'Not' *(Continued from page 2)*

one-third (30.6%) of the cohort received guideline-concordant care, defined as one biopsy and three PSA tests. Among the remaining 69.4% of men who received guideline-discordant care, biopsy represented the biggest gap; 53.6% received either no biopsy (31.3%) or no PSA test (15.8%), and 22.3% received neither.

Dr. Auffenberg stated, "AS involves an up-front agreement between the provider and patient. It does not mean 'forget about it.' It means you have cancer, and we're going to actively follow it. It's a management strategy, and biopsy is really the gold standard to have a really good idea of what's going on in the patient's cancer."

Scott Eggener, MD, co-

director of the Prostate Cancer Program at the University of Chicago Medical Center was asked to comment on the findings. He said, "A lot of men with prostate cancer on AS ultimately end up being followed by a non-urologist, and unfortunately, information on appropriate follow-up understandably isn't known amongst the primary care community."

He said, "Although some of the missed follow-up is patient-driven -- they just stop showing up, and they get too comfortable, there are also physicians who undoubtedly are not following or recommending the guidelines and probably aren't ordering the tests or biopsies perhaps as regularly as they should."

Urine Gene Assay Distinguishes High- vs. Low-Grade Prostate Cancer

A urine exosome three-gene expression assay discriminates high-grade prostate cancer from low-grade and benign disease and could help to reduce the number of unnecessary biopsies in men, according to new research.

"There are nearly two million biopsies done each year and only a small percentage (20-25%) contains high-grade prostate cancer. This suggests that many of these men could have avoided and/or delayed a biopsy, and not have been exposed to a diagnosis of indolent or low-risk disease along with the morbidity associated with the biopsy procedure," Dr. Michael Donovan, of the Icahn School of Medicine at Mt. Sinai, New York, told Reuters Health.

"Our study was one of the largest prospective trials designed for assessing the presence of high-risk prostate cancer on an initial biopsy.

Importantly, the results identified that from 27% to 37% of biopsies could potentially have been avoided with this assay," he said.

Dr. Donovan and colleagues conducted a training trial in which they compared biopsy outcomes with the performance of the ExoDx Prostate Intelliscore (Exosome Diagnostics) urine exosome assay plus standard of care (SOC) vs. SOC only at 22 US clinics.

The 499 patients in the study were eligible as being prostate cancer-free, 50 or older, and scheduled for prostate biopsy due to digital rectal examination (DRE) findings and/or having PSA levels between 2 and 20 ng/mL.

Of the 499 patients, 255 became the intended-use population in the training group, representing the same eligibility requirements except for PSA levels between 2 and 10 ng/mL. The researchers validated the prognostic score

Stacy Loeb, MD, a prostate cancer specialist from New York University and member of the AUA Public Media Committee, said the findings are consistent with those from a study her group conducted employing use of the SEER-Medicare database.

"One of the key questions that remain unanswered is, what is the optimal protocol to use for active surveillance? Now that more men are choosing AS, we must focus more efforts on identifying the best testing protocol for specific patient populations and ensuring sufficient follow-up."

Presented at the AUA 2016 Annual meeting, Abstract MP25-12

Medscape Medical News
9 May 2016

from the assay in 1,064 patients, of which 519 became the intended-use population in the validation group.

The team found the assay plus SOC to be associated with improved discrimination between Gleason score (GS) 7 or greater prostate cancer and GS6 or benign disease compared with SOC alone (area under receiver operating characteristic curve (AUC), 0.77 vs. 0.66, $p < 0.001$) for the 255 men in the training group. In the 519 men in the validation group, the assay plus SOC was also superior to SOC alone (AUC, 0.73 vs. 0.63, $p < 0.001$).

They calculated that 138 of the 519 biopsies (27%) in the validation group could have been avoided while missing 5% of patients with high-grade disease.

"A completely noninvasive, easy-to-obtain, first-catch urine specimen is able to pro-

(Continued on page 6)

Chemotherapy Conundrum for High-Risk Prostate Cancer

A randomized, phase III trial of adjuvant docetaxel in high-risk prostate cancer missed its primary endpoint but may still have impact on clinical practices, prostate cancer specialists reported at the 2016 American Urological Association (AUA) Annual meeting.

In an effort to inform decision-making about adjuvant chemotherapy for high-risk disease, the Department of Veteran Affairs sponsored Cooperative Trial 553 to evaluate docetaxel in the post-radical prostatectomy (RP) setting. Eligible patients had clinical T1-T2b disease and treatment by RP. High risk was defined as cancer not confined to the prostate, positive surgical margins associated with Gleason grade 8 to 10 disease, or a baseline PSA value >20 ng/mL.

All men underwent lymph node dissection and those with nodal metastases were ineligible for randomization.

Men who met entry criteria were randomized to six cycles of docetaxel plus prednisone or to observation. The primary endpoint was progression-free survival (PFS).

From 2006 to 2011, investigators enrolled and randomized 297 of the planned 400 men for the trial. Although the data and safety monitoring committee found no reason to stop the trial, the VA decided to halt patient accrual because of "resource issues." The two randomized groups did not differ significantly with respect to demographic or clinical characteristics. About a third of patients had Gleason grade 8 to 10 disease, a third had \geq T3b disease, and more than half had positive margins.

When the trial ended, men who received docetaxel after RP had a median PFS of 55.5 months vs. 45.6 months with

RP followed by observation. The difference translated to a hazard ratio for progression of 0.82 (95% CI 0.59-1.14, $P=0.24$, not significant).

However, prespecified subgroups at especially high risk — pathologic stage T3b and African American (AA) men — derived greater PFS benefits, Daniel Lin, MD reported. Men with \geq T3b disease (seminal vesicle invasion) had a statistically significant improvement in PFS, 47.2 vs. 29.2 months (HR 0.57, 95% CI 0.34-0.96, $P=0.03$).

In the AA subgroup, who accounted for a fourth of the total study population, the median PFS was 55.5 months with docetaxel and 32.7 months without, a difference that just missed the cutoff for significance (HR 0.54, 95% CI 0.29-1.01, $P=0.05$).

The negative primary outcome does not signal an end to evaluation of adjuvant docetaxel in the setting of high-risk prostate cancer.

"There are many other trials in preparation, and these data will certainly support those other trials that will be coming along, most of which will include androgen deprivation therapy (ADT)," said Lin, of the Seattle Cancer Care Alliance and the University of Washington. "In this study, patients did not receive ADT with docetaxel."

Despite missing the primary endpoint, the trial may still influence clinical practice.

"I think for the highest risk patients, it will come up in the discussion [of treatment options]," said Lin.

The trial will not support a case for an FDA-approved indication for docetaxel, but at the same time, "I would caution against a take-away of this as a negative phase III study," he continued.

"Patients with high-risk prostate cancer, including African Americans, will be interested in the results, and clinicians should be aware of them when discussing treatment options," agreed Sam Chang, MD, of Vanderbilt University.

High-risk prostate cancer remains a challenge, despite effective curative treatment for early-stage disease.

About half of all men with high-risk disease eventually have recurrence (primarily biochemical, or PSA, recurrence), for which no universal standard of care exists.

"Trials of adjuvant radiation therapy (RT) after RP have yielded mixed results with respect to overall survival," said Lin. Few studies have investigated cytotoxic chemotherapy alone. Trials of ADT with or without cytotoxic chemotherapy or RT have provided no clear therapeutic direction for patients with high-risk disease.

As a result, "the study was underpowered to detect the expected treatment effect," said Lin.

Adverse events in the docetaxel group were consistent with the drug's known toxicity. Grade 3/4 adverse events included neutropenia (43%), hyperglycemia (20%), infection (11%), and fatigue (5%). Febrile neutropenia occurred in 2% of the docetaxel arm.

Reference:

Lin D, et al "VA CSP#553: Chemotherapy after prostatectomy for high-risk prostate carcinoma: A phase III randomized study" AUA 2016; Abstract PL-LBA6.

MedPage Today
11 May 2016

Urine Gene Assay

(Continued from page 5)

vide useful information in the initial biopsy decision process. Our test adds meaningful new information for clinicians to share with patients in reaching an important decision about whether to continue monitoring or to proceed with a biopsy," Dr. Donovan stated.

"We do believe that the evidence from this prospective validation trial supports the incorporation of the ExoDx Prostate IntelliScore[®] assay in conjunction with other clinical factors, as a secondary or reflex test to aid the urologist and patient in the initial biopsy decision process. Importantly a number of the authors on this trial will also be involved in subsequent clinical utility and health economic studies utilizing this assay in clinical practice," he said.

"Supportive assays continue to be necessary to refocus our efforts for identifying clinically-significant disease while reducing the over-detection and over-treatment of low-risk prostate cancer," he added.

Dr. Hiten Patel of the James Buchanan Brady Urological Institute in Baltimore, co-author of an accompanying editorial, opined, "The efficacy of the assay is generally equivalent to other recent serum and urine tests evaluated in the past two years."

"Going forward, it will be important from the perspective of research ethics to assess the assay and similar tests in independent settings with data that is not directly gathered by a company involved with producing and marketing the test," he said.

Reuters Health Information
15 April 2016

Doctor Chodak's Bottom Line

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

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P1 – “USPSTF...” The 2011 Grade D recommendation by the US Public Services Task Force (USPSTF) against PSA screening upset a great many clinicians and patients. Now, an updated review will be undertaken to determine if that recommendation should be modified. Since no new studies will be performed, the question is whether the existing studies will lead to a different outcome. The most recent AUA recommendation has been to have a shared decision between the patient and doctor. It would be most helpful if a study would be done to evaluate both the frequency of and the amount of time devoted to this effort by clinicians. I doubt adequate time or effort is being committed to this need, so health experts are likely to be disappointed.

The Bottom Line: Many people will anxiously await the updated guidelines from the US public task force regarding screening.

P1 – “Prostate Cancer...” Our knowledge about active surveillance (AS) continues to expand but many unanswered questions remain. One of them is “What is the long-term risk of developing metastases?” Some data are now forthcoming with the report by Klotz and co-workers who analyzed the results of their AS study patients. They found that 10% of the men with Gleason 7 disease developed metastases with a follow-up slightly more than six years. Of course, this means that having any Gleason pattern 4 is not nearly as safe on AS as having only Gleason 6 disease. More analysis of these data is needed to identify those factors in men with

Gleason pattern 4 disease that are more predictive of disease progression. The results do not mean men with Gleason pattern 4 should avoid AS, but rather they should be made aware that it carries more risk compared to Gleason 6 disease.

The Bottom Line: Men with Gleason 7 cancer who are considering AS should be made aware of the risk of metastases at six years.

P1 – “Timing of...” A landmark study was recently reported by Duchesne et al in which men with a rising PSA after local therapy or untreated advanced disease were randomized to immediate ADT or delayed ADT given after a minimum of two years. They found that immediate ADT resulted in a statistically significant improvement in survival. Although immediate therapy reduced the death rate from 20% to 11%, it only improved overall survival by 5%, meaning that 20 men had to be treated to improve the survival of one man. Fortunately, morbidity was not significantly different but men receiving immediate ADT would obviously endure their side effects for a longer time.

The reason this study is so important is because until now doctors had no proof whether early ADT was worth doing. Only studies of men with metastatic disease clearly had improved survival from immediate treatment. Many men watched as their PSA increased without being advised to begin ADT.

Now men can be told with greater certainty that a rising PSA is worth treating. Caution is needed, however, until the data are further analyzed to provide answers

to the following questions: (1) Is a postsurgical PSA of 0.2 ng/mL the critical value for beginning ADT or could it work as well if it were started when the PSA was slightly higher? (2) Would intermittent ADT work equally well since a randomized study showed it had similar survival to continuous ADT in non-metastatic disease? Hopefully these answers are forthcoming.

The Bottom Line: Men with a rising PSA after local therapy or with untreated disease have an improved survival from early vs. delayed ADT.

P2 – “Bevacizumab...” An interesting but preliminary study found bevacizumab (Avastin®) added to androgen deprivation therapy (ADT) resulted in a lower failure rate than ADT alone in men with a rising PSA. One problem is that they used a non-rising PSA as a measure of success, which is not always a reliable predictor of long-term success. Nonetheless, patients will have to wait a number of years before additional research is done and we know whether or not this drug will be approved for advanced disease.

The Bottom Line: Bevacizumab shows promise in men with a rising PSA who are treated with ADT but until the proper study shows a survival benefit, it will only be available to men participating in a clinical trial.

P2 – “Active Surveillance...” The above study may be helpful to reduce another problem from AS reported by Auffenberg et al. In a large cohort of Michigan urologists, they found that a high percentage of the patients were not following the rec-

ommended protocol for follow-up. This was mostly a decline in serial biopsies. The reasons for this problem are not entirely clear. At this time there is no BEST protocol to follow for men on AS, and around the country practices vary. No study, however, has shown the importance of biopsies within a finite period of time. It seems unlikely that the doctor or the patient in these practices believes the cancer should be ignored.

The Bottom Line: For now, patient education about the risks and uncertainties needs to be emphasized to all men on AS and careful follow-up is needed to avoid missing the opportunity to cure a potentially life-threatening cancer.

P3 – “New FDA-Approved...” We have another curious article about HIFU. The FDA has previously determined that the data were not sufficient to approve High Intensity Focused Ultrasound for the treatment of low-risk prostate cancer. However, they have issued an unusual approval for tissue ablation. Does this mean that a man with prostate cancer can have the procedure as a treatment for his prostate cancer? That is entirely unclear. If a man does have prostate cancer, exactly what is a clinician going to tell the patient regarding the use of HIFU? Although the treatment has been used on thousands of patients throughout the world, the fact is no randomized study has compared it to other available therapies. It would seem this approval will create great confusion for patients if clinicians favoring HIFU provide misleading information to patients.

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New FDA-Approved Prostate Tool: Will You HIFU? (Continued from page 3)

success, according to Christian G. Chaussy, MD, professor of urology at University of Regensburg, Germany, and clinical professor of urology at the University of Southern California, in Los Angeles. "Three recent European studies show cancer-free and metastases-free survival rates in the 90% range at 10 years," he said. "It's a hope for the US; for the rest of the world, it is already reality."

But the reality of HIFU in the rest of the world is that its precise focus for the treatment of prostate cancer remains a matter of debate. In the more than 80 peer-reviewed publications on HIFU, reporting on 65,000 treatments worldwide, HIFU is used for a mix of whole-gland treatment and focal therapy.

"Oncologic and functional outcomes of whole-gland ablation have been established. Outcomes of focal

therapy have been shown to be durable. This could fill the gap between active surveillance and definitive radical therapy," according to Dr. Chaussy.

But Dr. Lawrentschuk noted that "large multicenter trials are lacking, there are different technologies and protocols, there is lack of consensus on ideal candidates, and there is a lack of follow-up biopsies, failure rates, and morbidity reporting." He added, "Canadian and Australian studies suggest there is high post-HIFU morbidity, including urinary incontinence and erectile dysfunction.

Why such disparity? Panelist Mark Emberton, MD, a HIFU expert from University College Hospital in London, UK said "HIFU requires a huge amount of back-up, sophistication, and expertise. I think we're at the very early stage of the refinement and development of this technology. We look forward to the time

when we can gain knowledge and experience from experts on this side of the Atlantic."

But the elephant in the room is payment. Lacking FDA approval of HIFU for the treatment of prostate cancer, "most third-party payers probably won't pay for it," predicted Victor W. Nitti, MD, from the NYU Langone Medical Center, who is a spokesperson for the AUA. "Patients are going to have to make decisions based on what urologists tell them, so urologists need to know as much as possible so they can advise their patients," he added.

But Dr. Koch thinks the movement will be largely patient-driven. "Many guys don't want their whole prostate out and they see this as a big win if it's reasonably effective in treating cancer," Dr. Koch said. There are a lot of people who want it."

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The Bottom Line

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The Bottom Line: Although HIFU is approved for tissue ablation, men should be very cautious about having their prostate cancer treated this way because it is not clear if it really improves survival.

P6 – "Chemo Conundrum..."

Another study providing confusing information was reported by Lin and co-workers who conducted a randomized trial of adjuvant docetaxel after radical prostatectomy (RP) in high-risk men. No significant improvement in progression-free survival was seen but African American (AA) men and men with pT3b cancer (seminal vesicle invasion) appeared to benefit. Docetaxel is not approved for this indication, but clinicians should mention these results when discussing treatment options with these men.

The Bottom Line: Adjuvant docetaxel post-RP appears to reduce the recurrence rate for AA men and pT3b disease.

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