Hot SHEET
Us TOO INTERNATIONAL Prostate Cancer Education and Support Network

INSIDE

AR-V7 Expression Predicts Prostate Cancer Outcomes

Expression of androgen-receptor splice variant 7 (AR-V7) on circulating tumor cells (CTC) is linked with superior survival on taxane therapy versus androgen receptor signaling (ARS)-directed therapies in men with castration-resistant prostate cancer, (CRPC) researchers report. Results were presented at the American Society of Clinical Oncology (ASCO) 2016 Annual Meeting, with simultaneous publication online in *JAMA Oncology*.

"The need for a predictive test to guide treatment selection has been an unmet need for a long time," Dr. Howard I. Scher from Memorial Sloan Kettering Cancer Center in New York City told Reuters Health by email. "The data presented shows the high specificity of a test result showing the presence of AR-V7 expression on CTCs and the lack of response to ARS-directed therapies, and the survival advantage provided by the use of taxanes."

In previous reports, AR-V7 expression was associated with resistance to ARS inhibitors (ARS-Is) but did not predict response to taxanes.

Dr. Scher and colleagues investigated the association between pre-therapy detection of AR-V7-positive CTCs with line of therapy and objective outcomes following treatment with ARS-I and taxanes in 161 men with metastatic CRPC.

The frequency of AR-V7-positive CTCs increased from 3% prior to first-line therapy to 18% prior to second-line therapy and 31% prior to third- or subsequent lines of therapy. As previously reported, AR-V7 expression on

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More High-Risk Pathology at Prostatectomy

Radical prostatectomy (RP) specimens with unfavorable pathology increased over nine years, but the reasons remain unclear, according to a study reported at the American Urological Association (AUA) 2016 Annual Meeting. Results were reported by Katherine Rotker, MD, of Brown University in Providence, RI.

Following US Preventive Health Services Task Force (USPSTF) 2009 and 2012 recommendations against PSA screening, the rate of RPs declined but the age of men undergoing RP did not change. There was a shift towards more Gleason 8-10 disease, and the frequency of organ-confined disease decreased.

Rotker reported findings from a comparison of pathologic findings at RPs performed at Brown during three time periods. The first group represented men who had RP from 2006 to 2008 (before USPSTF recommended against PSA testing in men ≥75). The second group captured the RP experience from 2009 to May 2012 (before USPSTF recommended against routine screening for men of any age). The third group represented the pathological findings at RP from May 2012 to May 2015 (following the 2012 USPSTF recommendation).

Rotker reported that:

- The number of RPs decreased from 561 in group 1 to 476 (15%) in group 2 to 311 (35%) in group 3
- Mean age of men undergoing RP remained stable at 60 through the study period
- The proportion of specimens with pure Gleason grade 6 decreased from 46% to 24% (P<0.001) to 12% (P <0.001)

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Short-Term Androgen Suppression Benefits Men after Prostatectomy

Adding short-term androgen deprivation treatment (ADT) to salvage radiotherapy (RT) benefits men with a rising PSA after a radical prostatectomy (RP) that rendered PSA undetectable, researchers reported in the *Lancet Oncology*, online 6 May 2016.

How best to treat rising PSA concentrations after RP is an "urgent clinical question," according to Dr. Christian Carrie of Centre Leon Berard, Lyon, and colleagues. According to Dr. Carrie, about a third of men will relapse and fewer than half will be free of metastases at 10 years. Although salvage RT (SRT) delays the need for more aggressive treatment, such as long-term ADT, "fewer than half of patients benefit from it," the team writes.

To investigate the effect of adding short-term ADT at the time of SRT on outcomes and overall survival, Dr. Carrie and colleagues conducted a multicenter, randomized, open-label phase 3 trial, GETUG-AFU16. Men who had rising PSA of 0.2 to <2.0 ng/mL after a post-RP period when PSA was undetectable, and who had no evidence of clinical disease, were eligible.

A total of 374 men were randomly assigned to RT (five days a week for seven weeks) and 369 to RT plus ADT (goserelin 10.8 mg subcutaneously on the first day of RT and again three months later). The researchers found that men assigned to RT plus ADT were significantly more

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A Phase III Study Comparing Intermittent vs. Continuous Docetaxel Therapy in Patients with Castration-Resistant Prostate Cancer

Cash H, Steiner U, Heidenreich A, et al

J Clin Oncol 34, 2016 (suppl); Abstract 5005 presented at the 2016 Annual ASCO Meeting

Background: A randomized phase III study investigating the non-inferiority of intermittent vs. a continuous docetaxel treatment for men with castration-resistant prostate cancer (CRPC).

Methods: 187 patients were randomized to either an intermittent or a continuous docetaxel treatment until discontinuation (docetaxel application in both arms was weekly 35mg/m^2 or three-weekly 75mg/m^2). The intermittent arm received docetaxel for one study sequence of 12 weeks and then paused until clinical disease progression, defined by one of the following criteria: increased serum PSA > 4ng/mL with a 50% increase over baseline level, radiological or symptomatic progression. The primary endpoint was one-year survival, which was tested for non-inferiority (efficacy margin 12.5%). Secondary endpoints were overall survival (OS), progression-free survival (PFS), median time to treatment failure (TTF) and toxicity. Final recruitment was not reached.

Results: Of 156 eligible patients, 78 were allocated to each arm. One-year survival was 72.6% in the continuous arm vs. 75.8% in the intermittent arm and median OS 18.3 months (95% CI: 15-21.5) vs. 19.3 months (95% CI: 4.7-6.1) (P= 0.535). Intermittent treatment met the non-inferiority criteria in one-year survival (difference to lower 95% CI: -0.1201), but not for OS, according to the result of a post-hoc analysis. The differences between the study arms in PFS and TTF were not significant. The median treatment holiday in the intermittent arm was 15 weeks (range 1-69), or 38% of the overall treatment duration. Safety profiles of both study arms were comparable.

Conclusions: Intermittent docetaxel was non-inferior to continuous therapy in one-year survival. It was well tolerated and may present a treatment option for men with CRPC.

Five-Year Biochemical Results, Toxicity, and Patient-Reported Quality of Life After Delivery of Dose-Escalated Image Guided Proton Therapy for Prostate Cancer

Bryant C, Smith TL, Henderson RH, et al

Int J Radiat Oncol Biol Phys 95: 422-434, 2016

Purpose: To report clinical outcomes in patients treated with image guided proton therapy (IGPT) for localized prostate cancer.

Methods and Materials: The medical records of 1327 men were reviewed. Each man was enrolled on an outcomes tracking study. Dual enrollment on a prospective clinical trial was allowed. Each man was treated for localized prostate cancer with IGPT at our institution between 2006 and 2010. Ninety-eight percent of men received 78 Gy (radiobiological equivalent [RBE]) or higher; 18% received androgen deprivation therapy. Five-year freedom from biochemical progression (FFBP), distant metastasis-free survival, and cause-specific survival rates are reported for each risk group. Data on patient-reported quality of life and high-grade toxicities were prospectively reported. Multivariate analysis identified clinical predictors of BP and urologic toxicity.

Results: Median follow-up was 5.5 years. Five-year FFBP rates were 99, 94, and 74% in low-, intermediate-, and high-risk patients, respectively. Actuarial five-year rates of late grade 3+ Common Terminology Criteria for Adverse Events, version 4.0, gastrointestinal and genitourinary toxicity (GU) were 0.6 and 2.9%, respectively. Multivariate analysis showed a significant correlation between grade 3+ GU toxicity and pre-IGPT prostate reductive procedures (P <0.0001), prostate volume (P=0.0085), pre-IGPT α-blockers (P=0.0067), diabetes (P=0.0195), and dose-volume histogram parameters (P=0.0208). The median International Prostate Symptom Scores pre-IGPT and at five years post-IGPT were seven and seven, respectively. Mean Expanded Prostate Cancer Index Composite (EPIC) scores significantly declined for sexual summary for men not receiving ADT between baseline and five years.

Conclusions: IGPT provided excellent biochemical control rates for men with localized prostate cancer. Actuarial rates of high-grade toxicity were low. From pretreatment to five years of follow-up, a significant decline was found only in mean EPIC sexual summary scores. Prospective clinical studies are needed to determine the comparative effectiveness of PT and other RT strategies.

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

"Attending Religious Services Could Improve Life Expectancy??!!"

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:

One of the largest prospective studies to ever address this issue found significantly lower risks of dying from cardiovascular, cancer and all causes for those that regularly attended religious services.[1] Obviously, more research is needed (especially in men), but to simply say this is fascinating is an understatement. So, why aren't people talking about it? I think it may be because those that read this article did not closely focus on the overall, personal message.

I was very surprised that the findings of a study of this magnitude failed to receive attention. Why? Is it because this is not a PC topic and people would feel uncomfortable talking about it? I think so, but since the only time I really care about focusing on being PC is when that acronym applies to my "Personal Computer" not working right, let's focus on this incredibly interesting study.

Nearly 75,000 women were included in what is arguably one of the most robust, ongoing US studies called the "Nurses' Health Study." The researchers found a very consistent reduction in the risk of dying from cardiovascular disease, cancer and all causes of death in those who attended religious services more than once a week compared to those who do not attend religious services at all. And, there are 16 years of follow-up thus far with these participants. This means that this study is one of the longest and most thorough studies that has addressed this subject. Even after the results were adjusted for depression, smoking, social support or optimism (or blah blah blah), this association remained. I think it is amazing that "social support" was arguably one of the best explanations for a portion of these findings.

What more should I say here? If I suggest that more people should attend religious services for a health benefit, then I will get some hate and love mail. What if I suggest that attending religious services has not been studied enough so you can get these benefits in other ways? Either way, I think that I will get some love mail and some hate mail. Hmmmm… what should I do here? I will tell you that at no other time in my life have I witnessed human beings yearning for some type of human contact; be it time with family, doctor, friends, etc., it all seems less than before and just trying to reach a human, be it some person on the phone at a business seems almost impossible. Today, we seemed to have painted ourselves into a non-human communicative corner, perhaps due to fast-paced lives and our advanced technology.

So, where can we regularly go to find optimism, support, social networking, selfless behavior, friendship, and love? Is it volunteering on a regular basis? Of several options, one is attending religious services; another is is to become more involved with family and community in some way that brings us meaning. I believe you should pursue whatever endeavor that can increase your social support. I will say this again: this is another reason why I believe most cancer patients should attend cancer support groups. I also believe that whatever it takes to remain socialized and human is needed for humanity and perhaps longevity and health for some folks.

Where do you find inspiration and support? If you answer the i-Phone or computer or TV then perhaps I think you might want to look in another location. Am I suggesting that you should go to a church, synagogue, temple, mosque, etc.? I don't know what the heck I am suggesting, except to say to focus on the forest over the tree when considering the results of this research. Social support, staying connected, support groups, family, religion, friendship, volunteering …who knows in reality if it will really prove to increase life expectancy, but in reality, it does not matter because at the very least, we have always known it can increase your quality of life. Did we really need research to prove that fact?

Reference:

1. Li S, Stampfer M, Williams DR, et al. Association of religious service attendance with mortality among women. JAMA Intern Med 176: 777-785, 2016.

More High-Risk Pathology at Prostatectomy *(Continued from page 1)*

- Frequency of Gleason 8-10 increased from <1% to 8.40% (P <0.001) to 13.2% (P=0.04)
- Proportion organ-confined disease decreased from 84.5% to 71.4% (P <0.01) to 52.7% (P=0.01)
- Proportion focal extraprostatic extension (ECE) increased from 13.6% to 20.8% (P=0.002) and then leveled off
- Proportion established ECE increased from 1.25% to 8% (P<0.001) to 17% (P <0.001)
- Frequency of pathologic stage T3 increased from 15.5% to 29.2% (P <0.001) to 38.26% (P <0.01)

The proportion of men with positive surgical margins increased from group 1 to group 2, and then declined to less than the baseline level in group 3. The frequency of seminal vesicle involvement increased from 4.1% to 7.4% and the frequency of positive lymph nodes increased from 2.5% to 6.36%. However, analysis was limited by small numbers, said Rotker.

"It's not clear if the changes at RP are due to lack of PSA screening, more adherence to active surveillance (AS) protocols, or increased use of surgery in high-risk disease," said Rotker. "Most likely, it involves a combination of all three factors. "The information gained from screening is being applied differently, and a very different population of patients is being brought to surgery. It may be time to revisit the number-needed-to-treat (NNT) and benefit of PSA screening."

Reference:

Rotker K, et al. Abstract PD03-05 presented at the 2016 AUA Annual Meeting,

MedPage Today, 17 May 2016

Acute Toxicity and Quality of Life in Patients with Prostate Cancer Treated with Protons or Carbon Ions in a Prospective Randomized Phase II Study – The IPI Trial

Habl G, Katayama S, Kessel KA, et al

Int J Radiat Oncol Biol Phys92: 435–443, 2016

Purpose: The purpose of this study was to compare safety and feasibility of proton therapy with that of carbon ion therapy in hypofractionated raster-scanned irradiation of the prostate, in a prospective randomized phase 2 trial.

Methods and Materials: In this trial, 92 men with localized prostate cancer were enrolled. Patients were randomized to receive either proton therapy (arm A) or carbon ion therapy (arm B) and treated with a total dose of 66 Gy (relative biological effectiveness [RBE]) administered in 20 fractions (single dose of 3.3 Gy[RBE]). Men were stratified by the use of anti-hormone therapy. Primary endpoint was the combined assessment of safety and feasibility. Secondary endpoints were specific toxicities, prostate-specific antigen progression-free survival (PFS), overall survival (OS), and quality of life (QoL).

Results: Ninety-one patients completed therapy and have had a median follow-up of 22.3 months. Among acute genitourinary toxicities, grade 1 cystitis rates were 34.1% (39.1% in A; 28.9% in B) and 17.6% grade 2 (21.7% in A; 13.3% in B). Seven patients (8%) required urinary catheterization during treatment due to urinary retention, five of whom were in arm A. Regarding acute gastrointestinal toxicities, two men treated with protons developed grade 3 rectal fistulas. Grade 1 radiation proctitis occurred in 12.1% (13.0% in A; 11.1% in B) and grade 2 in 5.5% (8.7% in A; 2.2% in B). No statistically significant differences in toxicity profiles between arms were found. Reduced QoL was evident mainly in fatigue, pain, and urinary symptoms during therapy and six weeks thereafter. All European Organization for Research and Treatment of Cancer QLQ-C30 and -PR25 scores improved during follow-up.

Conclusions: Hypofractionated irradiation using either carbon ions or protons results in comparable acute toxicities and QoL parameters. We found that hypofractionated particle irradiation is feasible and may be safe. Due to the occurrence of gel in the rectal wall and the consecutive occurrence of two rectal fistulas, we stopped using the insertion of spacer gel. Longer follow-up is necessary for evaluation of PFS and OS. (Ion Prostate Irradiation (IPI); NCT01641185; ClinicalTrials.gov.).

FDA Approves Diagnostic Agent for Recurrent Prostate Cancer

The US Food and Drug Administration (FDA) has approved ^{18}F-fluciclovine (Axumin, Blue Earth Diagnostics), an injectable radioactive diagnostic agent that is used to detect recurrent prostate cancer.

The agent is approved for use with PET imaging in men with suspected disease recurrence on the basis of elevated PSA levels after previous treatment.

Fluciclovine is a synthetic amino acid, and has been developed for the PET imaging of cancers for which other PET imaging agents have not been widely adopted, according to the manufacturer.

It is actively transported by certain amino acid transporters and has demonstrated high uptake in prostate cancer, as well as glioma cell lines and xenografts.

The FDA based its decision on results from two studies that evaluated the safety and efficacy of fluciclovine.

In the first study, 105 fluciclovine scans of men with suspected prostate cancer recurrence were compared with the histopathology that was obtained by prostate biopsy and biopsies of suspicious imaged lesions.

Onsite radiologists read the scans initially, and then the scans were read by three independent radiologists in a blinded study.

The second study compared fluciclovine with ^{11}C-choline, an approved PET scan imaging test, in scans conducted on men with median PSA values of 1.44 ng/mL. The three onsite independent radiologists in the first study also reviewed the fluciclovine scans in this second blinded study.

"The results of the independent scan readings were generally consistent with one another, and confirmed the results of the onsite scan readings," the FDA noted. "Both studies supported the safety and efficacy of [fluciclovine] for imaging prostate cancer in men with elevated PSA levels following prior treatment," the agency said.

Adverse events related to fluciclovine were minimal, and the most commonly reported events were injection-site pain, redness, and a metallic taste in the mouth.

Medscape Medical News
31 May 2016

AR-V7 Expression

(Continued from page 1)

CTCs was associated with worse outcomes, including shorter radiographic progression-free survival (rPFS), shorter time on therapy, and shorter overall survival (OS) in men treated with ARS-Is.

In contrast, among men treated with taxanes, time on therapy and rPFS did not differ by pre-therapy AR-V7 status, but OS was worse for those with AR-V7-positive CTCs than for those with AR-V7-negative CTCs.

Men with AR-V7-positive CTCs had significantly longer median survival with taxanes (8.9 months) than with ARS-Is (4.6 months), even though taxanes tended to be administered later and when disease burdens were greater. Men with AR-V7-negative CTCs had similar outcomes after ARS-Is and taxanes.

"Every patient harboring AR-V7-positive CTCs was resistant to treatment with ARS-Is, including three men with AR-V7 positivity only on CK-negative CTCs, cells not detectable with EpCAM-based CTC capture method including the previously reported AR-V7 mRNA transcript detection approaches," the researchers note.

"Taken together," they conclude, "our results, and those of others, suggest that men in whom AR-V7-positive CTCs are detected would be better served with an approved taxane over abiraterone or enzalutamide."

"Of particular importance was the demonstration of clinical utility – the clinical benefit (superior outcome) for the patient by using the test result to inform the decision incorporating the test result relative to non-use of the test result," Dr. Scher said.

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Cabazitaxel vs. Docetaxel in Chemotherapy-Naïve (CN) Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC): A Three-Arm Phase III Study (FIRSTANA)

Sartor AO, Oudard S, Sengelov L, et al

J Clin Oncol 34, 2016 (suppl); abstract 5006 presented at the 2016 ASCO Annual Meeting

Background: The Phase III TROPIC study (NCT00417079) reported significant improvement in overall survival (OS) for cabazitaxel (C) 25 mg/m^2 IV Q3W plus prednisone 10 mg PO QD (P) vs. mitoxantrone plus P in mCRPC pts previously treated with a docetaxel (D)-containing regimen. The FIRSTANA study examined if C 20 mg/m² (C20) or 25 mg/m² (C25) IV Q3W plus P is superior to D 75 mg/m² (D75) IV Q3W plus P in terms of OS in CN mCRPC pts.

Methods: In this multinational, open label phase III study, mCRPC pts, ECOG PS 0-2, who had progressed after castration were randomized 1:1:1 to C20, C25 or D75 IV Q3W plus P. The primary endpoint was OS. Key secondary endpoints were safety, progression-free survival (PFS), tumor PFS, tumor response (RECIST 1.1), PSA response, PSA PFS, pain response, pain PFS, time to skeletal-related events (SRE) and health-related quality of life (HRQOL).

Results: Between May 2011 and April 2013, 1168 pts were randomized (C20=391, C25=389, D75=388). Baseline demographics and disease characteristics were similar across cohorts. The median number of treatment cycles was 9 for all dose groups. In the ITT analysis, median OS was 24.5 months for C20, 25.2 months for C25 and 24.3 months for D75. HR for C20 vs. D75 was 1.009 (0.85 to 1.197, p=0.9967) and for C25 vs. D75 was 0.97 (0.819 to 1.16, p=0.7574), indicating that C20 and C25 were not superior to D75 in terms of OS. PFS was 4.4 months for C20, 5.1 months for C25 and 5.3 months for D75 (NS). Tumor responses were superior in C25 (41.6%) compared to D75 (30.9%), p=0.0370. Other secondary endpoints did not significantly differ across dose groups. Adverse events (AEs) grade 3-4 were 41.2% in C20, 60.1% in C25 and 46.0% in D75; pts discontinuing treatment due to an AE were 25.2% in C20, 31.7% in C25 and 33.9% in D75. Febrile neutropenia, diarrhea and hematuria were more frequent in C25; peripheral neuropathy, peripheral edema, alopecia and nail disorders were more frequent in D75.

Conclusions: C20 and C25 did not demonstrate superiority for OS compared to D75 in CN mCRPC pts. Among secondary endpoints only tumor responses were significantly superior for C25. AEs were less frequent in C20 for most categories. (Clinical trial information: NCT01308567)

Adiposity Linked to Aggressive Prostate Cancer and Death

Obese men (high body mass index [BMI] and large waist circumference), have a greater risk of both high-grade, aggressive prostate cancer and prostate cancer death than men with normal BMI and waist circumference, reveals new data from a large European study presented at the 2016 European Obesity Summit (EOS).

The study of over 140,000 men from eight countries showed that there was a linear association between BMI and waist circumference and high-grade prostate cancer and prostate cancer death, with the risks increasing by more than 10% with each stepwise increase in adiposity. Another notable finding from the investigation was that, paradoxically, the overall risk of prostate cancer was lower for men with a higher BMI and those

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Short-Term ADT Benefits Mean Post-RP *(Continued from page 1)*

likely than men in the RT-alone group to be free of PSAF or clinical progression at five years (80% vs. 62%; hazard ratio 0.50; P <0.0001).

Men receiving short-term ADT had similar late adverse events as did those who received RT alone. The most frequently occurring acute adverse events due to ADT were hot flushes, sweating, or both in the RT plus ADT group vs. none in the RT-alone group. The most common late adverse events of grade 3 or worse were genitourinary events and sexual disorders.

Dr. Anthony V. D'Amico of Brigham and Women's Hospital and Dana Farber Cancer Institute, Boston and author of an accompanying editorial, added, "This is a setting that's not uncommon because, particularly in today's world, more people are getting operated on for more-advanced prostate cancer. This is a result of the decline in PSA screening since the US Preventive Services Task Force recommended against such screening in 2012.

A previous study, RTOG-9601, was recently updated with 12.3 years of follow-up, according to Dr. D'Amico. However, when first reported, its follow-up time was similar to that of the GETUG trial, and the results were also "very, very similar" to those of GETUG. However, in contrast to the GETUG trial, RTOG-9601 included men whose post-RP PSA level was still detectable.

"Within that context, six months of an LHRH agonist, as prescribed in the GETUG study, will likely become the preferred option for men with a rising post-RP PSA, with the proviso that the PSA becomes undetectable following RP as in the GETUG study," Dr. D'Amico said.

He continued, "Physicians in the US are not likely to prescribe 150 mg of bicalutamide, even though it showed a survival benefit in RTOG-9601. That dose is not FDA approved... so even if someone wanted to prescribe it... there could be an insurance coverage issue."

Dr. Carrie told Reuters Health by email that he agreed with Dr. D'Amico's comments regarding the management of patients, given the results of the two trials: "Probably a shorter duration of androgen deprivation combined with salvage RT can be proposed for men with GETUG 16 criteria (PSA less than 1ng/mL and life expectancy greater than 12 years) and keep the option of longer androgen therapy, as in the RTOG trial, for patients with worse prognostic factors, such as PSA greater than 1ng/mL."

Reuters Health,
8 May 2016

Adiposity Linked to Aggressive Prostate Cancer and Death *(continued from page 5)*

with a larger waist circumference.

To examine the association between anthropometric factors and later prostate cancer risk, Dr. Aurora Perez-Cornago at the Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, UK, the lead researcher and colleagues examined data on 141,896 men (mean age 52 years) from Italy, Spain, the UK, the Netherlands, Greece, Germany, Sweden, and Denmark who were participating in the European Prospective Investigation into Cancer and Nutrition study.

They gathered data on height, BMI, and waist circumference and determined the risk of prostate cancer and prostate-cancer death using Cox regression analysis, stratified by recruitment center and adjusted for education level, smoking, marital status, diabetes, and physical activity.

Over a mean follow-up of 14 years, there were 7,022 incident cases of prostate cancer, 740 cases of high-grade prostate cancer, and 931 prostate cancer deaths.

The risk of all grades of prostate cancer was significantly lower among men in the highest quintile of BMI than in the lowest, at a hazard ratio (HR) of 0.90 (P <0.001), and among men with the highest vs. the lowest quintile of waist circumference, at a HR of 0.92 (P=0.013).

However, men in the highest quintile of BMI had a trend for an increased risk of high-grade prostate cancer vs. those in the lowest quintile, at a HR of 1.30 (P=0.125), and a significantly increased risk of prostate cancer death, at a HR of 1.35 (P=0.013).

The highest quintile of waist circumference was, compared with the lowest quintile, associated with a significantly increased risk of both high-grade prostate cancer, at a hazard ratio of 1.46 (P=0.003), and prostate cancer death, at a HR of 1.55 (P <0.001).

The researchers found that these increases in risk translated into a 10% increased risk of high-grade prostate cancer for every 5 kg/m^2 increase in BMI and a 13% increased risk for every 10 cm increase in waist circumference. In addition, every 5 kg/m^2 increase in BMI was linked to a 14% increased risk of fatal prostate cancer, while every 10 cm increase in waist circumference was associated with an 18% increased risk of prostate cancer death.

Dr. Perez-Cornago, PhD, explained that, when they initially analyzed the data, they realized that there were differences in incidence by cancer grade. She said, "That forced us to divide the study in those that have high-grade and low-grade disease, so we can't actually take into account the result for total prostate cancer."

The team concludes in a press release: "The findings from this large prospective study show that the association between body size and prostate cancer is complex and varies by disease aggressiveness; men who have greater adiposity have an elevated risk of high-grade prostate cancer and prostate cancer death. Our results are in line with health advice for other non-communicable diseases. Men should try to maintain a healthy weight."

Commenting, Jason Halford, PhD, of the European Association for the Study of Obesity and the University of Liver-

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Prospective Evaluation of ^{68}Gallium-PSMA Positron Emission Tomography/Computerized Tomography for Preoperative Lymph Node Staging in Prostate Cancer

van Leeuwen PJ, Emmett L, Ho B, et al

BJU Int 21 May 2016; Epub ahead of print

Conventional imaging techniques are inadequate for lymph node staging in prostate cancer (PC). This study aims to assess the accuracy of ^{68}Ga-PSMA positron emission tomography/computed tomography (PET/CT) for lymph node (LN) staging in intermediate and high-risk PC.

From April to October 2015, 30 patients with intermediate (n=3) or high-risk (n=27) PC were prospectively enrolled. Patients underwent preoperative ^{68}Ga-PSMA PET/CT. Both visual and semi quantitative analysis was undertaken. Subsequently, all patients underwent a radical prostatectomy (RP) with an extended pelvic lymph node dissection (eLND). Sensitivity, specificity, positive and negative predictive value (PPV and NPV) for LN status of ^{68}Ga-PSMA were calculated using histopathology as reference.

Eleven patients (37%) had lymph node metastases (LNMs), 26 LNMs were identified in the 11 patients. On a patient analysis, ^{68}Ga-PSMA PET/CT has a sensitivity of 64% for the detection of LNMs, specificity was 95%, PPV was 88%, and NPV was 82%. In total, 180 LN fields were analyzed. For the LN-region-based analysis, the sensitivity of ^{68}Ga-PSMA PET/CT for detection of LNMs was 56%, specificity was 98%, PPV was 90% and NPV was 94%. Mean size of missed LNMs was 2.7mm. Receiver operating characteristic (ROC) analysis demonstrated high accuracy of SUV max for the detection of LNMs, AUC 0.915 (95%CI 0.847-0.983); optimum SUV max was 2.0.

In men with intermediate to high-risk PC, ^{68}Ga-PSMA PET/CT has a high specificity and a moderate sensitivity for LNM detection. ^{68}Ga-PSMA PET/CT has the potential to replace current imaging for LN staging of patients with PC scheduled for RP.

AR-V7 Expression

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"It bears emphasizing that men with AR-V7-positive CTCs were not more sensitive to taxane than AR-V7-negative tumors, but the authors appropriately underscore that it is the ability of the assay to direct patients away from ineffective therapy that has the greatest potential for benefit," write Dr. R.B. Montgomery and Dr. Stephen R. Plymate from the University of Washington, Seattle, in an accompanying commentary.

If the differences in response to taxanes in the study by Scher et al are confirmed in prospective trials, AR-V7 protein in CTCs will provide an extremely useful positive response biomarker for taxane therapy, the editorial concludes.

Ultimately, this article presents further evidence that AR-variant expression in CTCs may be an important marker to direct therapy and potential targets for therapeutic intervention.

Reuters Health
10 June 2016

Doctor Chodak's Bottom Line

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 *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 – More High-Risk… Men deciding whether or not to go on active surveillance (AS) are faced with the prospect of either being over-treated or missing out on a potentially curable therapy. Although efforts are in progress to help patients make the right decision, ultimately this problem will likely persist. The study by Rotker and coworkers found that men who delayed therapy were more likely to have worse pathological findings than those undergoing immediate therapy. There are several factors that may be contributing to those results. Importantly, however, with a modest follow-up time, the likelihood of a rising PSA was not significantly higher in a matched cohort of men who were treated immediately. More follow-up is needed to more clearly define the added risk of delaying treatment on overall survival.

The Bottom Line: Men who choose AS and later undergo RP are more likely to have adverse pathology, but so far it is unclear if that will translate into a higher mortality.

P1 – AR-V7 Expression… Many cancer patients ask, "Why do some treatments work for some patients and not for others?" Medical researchers have been devoting enormous amounts of time and energy seeking an answer to that question. The article by Scher and coworkers is one example to show that progress is being made. They studied a protein variant of the androgen receptor called AR-V7 present on circulating tumor cells (CTCs) from men with CRPC. If the variant was present, men responded well when treated with docetaxel but were less likely to respond to the newer antiandrogens abiraterone and enzalutamide. Availability of this test to identify patients unlikely to benefit from the newer agents would be a great benefit for patient care. More studies are needed to validate this association.

The Bottom Line: A protein variant, AR-V7 may be very helpful in identifying which men should not receive enzalutamide or abiraterone and instead proceed to docetaxel chemotherapy.

P1 – Short-Term ADT… Studies have shown a small but significant benefit to RT for a rising PSA after RP. Since androgen deprivation therapy (ADT) added to external RT improves survival compared to RT alone for men with intermediate- and high-risk disease, it seems reasonable to ask whether adding ADT to salvage RT would also be beneficial. The randomized study reported by Carrie et al suggests a benefit in terms of biochemical outcomes can occur. However, because survival data was not reported, no firm conclusion can be drawn. Only time will tell.

The Bottom Line: Adding ADT to salvage RT may benefit patients but longer follow-up is needed before valid conclusions are possible.

P2 – A Phase III… For most urologists, chemotherapy is something to avoid primarily because they believe that in some cases side effects can be worse than the disease. For men with castration-resistant prostate cancer (CRPC) treated with docetaxel, traditionally the drug is continued until disease progression, regardless of how well they were responding. Whether or not patients could do just as well by limiting the duration of chemotherapy was a question rarely asked. In this issue, the study published by Cash et al reported results in 178 men who were randomly assigned to standard docetaxel therapy every 3-4 weeks or intermittent therapy where treatment was stopped after about 12 weeks and then restarted when CRPC progressed. Importantly, the authors found that intermittent docetaxel administration was not inferior to continuous therapy. This is an important finding because it means that many men may be able to reduce the amount of chemotherapy they receive without compromising their outcome.

The Bottom Line: CRPC patients receiving docetaxel may respond just as well when it is administered on an intermittent or continuous schedule.

P2 – Five-Year Biochemical… Another report on proton-beam radiotherapy (PBRT) presents overall efficacy data that is much more incomplete compared to data reported with other forms of RT. The study by Bryant provides us with data on a LARGE cohort of men showing biochemical data with a median follow-up of only 5.5 years. As I have said before, short-term PSA data is not a valid surrogate for long-term survival. I personally find it very disappointing that the authors reported results in a great many men (1,327) and then conclude by saying, "Prospective clinical studies are needed to determine the comparative effectiveness of PT and other radiation treatment strategies." I wonder why the researchers chose to continue accumulating patients without any possibility of knowing its true value and not do the study we so desperately need?

The Bottom Line: It remains; no well done studies prove that PBRT is safer or more efficacious. Given additional inconclusive data in this report, the same question exists; **is PBRT worth the cost**?

P4 – Acute Toxicity and Quality… And if that issue isn't enough, we have a new report about another form of particle radiation. Habl et al compared PBRT to carbon ion RT and reported similar toxicity but did not report the impact on cancer control. Some disadvantages of carbon ion include a higher potential for side effects, an inability to direct the beam in the same way it can be done with PBRT and a cost that is two to three times higher than other RT methods. Let's hope that thousands of men are not treated with carbon ion RT before a proper study is done to determine if this form of RT is worth giving.

The Bottom Line: Carbon ion therapy is another particle RT that may have a similar safety profile as PBRT, but as of yet, no advantage in treating prostate cancer has been demonstrated.

P4 – FDA Approves… Men with a rising PSA after radical prostatectomy (RP) or RT are challenged to know the location(s) of cancer recurrence. In the past, a ProstaScint scan was used but it was not very accurate when performed at very low post-RP

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PSA levels when salvage RT is most effective. More recently, PET scanning has been used and a new agent called Axumin has just been approved by the FDA to help identify recurrent disease. Patients should be cautious, however, because the accuracy of the results from clinical trials are not very good for detecting cancer in the area that matters most, the prostate bed. Patients are most likely to benefit from RT if recurrence is only in the prostate bed. When cancer is detected elsewhere, RT is seldom appropriate. The combined false positive rate and false negative rates in one of the clinical studies that supported FDA approval ranged from 26-31%. In a second study, three reviewers found agreement between Axumin and choline PET scans in 61-77% of cases but pathological confirmation was not required. It seems that being wrong 30% of the time is okay with the FDA!

The Bottom Line: Axumin is a new imaging agent for evaluating a rising PSA after RP or RT, but the accuracy, unfortunately, is not very high.

P5 – Cabazitaxel vs... The standard therapy for CRPC has been docetaxel. Another taxane, cabazitaxel, was FDA approved for treating men with progressive CRPC on docetaxel. A question has been raised whether cabazitaxel might be more effective as primary therapy. A large randomized study by Sartor et al attempted to answer that question and results showed no improvement in survival. However, it did appear that adverse effects were less common with cabazitaxel. More information is needed to determine whether this approach is reasonable for men with CRPC. For now, the FDA-approved use for cabazitaxel is docetaxel failure.

The Bottom Line: Cabazitaxel does not offer improved survival compared to docetaxel, but it may have fewer side effects.

P6 – Prospective... RP for men with high-risk prostate cancer is of questionable value because there is a high risk of lymph node metastases. If the presence of lymph nodes metastases were known, it would spare men from RP and direct them to RT instead. The data from Van Leeuwen et al suggests that performing a Gallium PET scan can identify men who lack lymph node metastases with a specificity of 98% (true negative/true negative plus false positive). Unfortunately, the sensitivity was not so good. This finding means that men with high-risk disease that have a negative Gallium scan may benefit from RP.

The Bottom Line: Gallium-PET scan may be helpful in men with high-risk prostate cancer to identify those unlikely to benefit from RP.

Adiposity and PCa

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pool, UK, said that this sort of study is "very, very important" because it shows that a lot of the increasing health issues in the aging population linked to cancer are "related to lifestyle factors that lead to weight gain."

He noted: "So there is a clinical imperative to manage individuals, but there's also a population-based imperative, because you've got to have both a population and an individual approach to deal with this, and these data tell me that we need to be doing a great deal more on both."

Presented at EOS 2016, 2 June 2016; Poster PO1.077

Medscape Medical News
2 June 2016

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