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Hot SHEET

Us TOO INTERNATIONAL Prostate Cancer Education and Support Network

New Look at Old Data Confirms Mortality Benefit from PSA Screening

But Analysis Doesn't Address Harms from Screening and Subsequent Treatment

Prostate cancer (PCa) screening resulted in a lower risk of PCa death for older men, according to pooled data from two pivotal trials that shaped recent PSA testing recommendations.

"Compared with men not screened, estimated risk of PCa death was cut by 25-31% in intervention groups of the European Randomized Study of Screening for Prostate Cancer (ERSPC) and by 27 to 32% in the Prostate, Lung,

Colorectal and Ovarian Cancer Screening Trial (PLCO)," reported Alex Tsodikov, PhD, of the University of Michigan, and colleagues.

Moreover, there was a 7 to 9% reduced risk of PCa death per year of mean lead times, or the average time by which diagnosis is advanced by screening vs. no screening. These extended analyses were published online ahead of print in the *Annals of Internal Medicine*.

Notably, they did not address potential harms from screening and follow-up procedures. Nevertheless, the analyses may add more fuel to the fire in the ever-evolving debate about the merits of PCa screening. While the U.S. Preventive Services Task Force (USPSTF) recommended against screening in 2012, a draft recommendation statement from April 2017 supported "discussion-backed" decisions
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Patients with High-Risk Prostate Cancer May Benefit "Equally" from Two New Treatments

Patients with high-risk prostate cancer (PCa) starting long-term hormone therapy (HT) may benefit from two new treatments, according to late-breaking results from the STAMPEDE trial presented at the ESMO 2017 Congress in Madrid. Long-term HT alone has been the standard of care (SoC) for men with high-risk locally advanced or metastatic PCa since the 1940s.

STAMPEDE is a platform protocol using a multi-arm, multi-stage design to efficiently investigate a number of new treatments vs. SoC in men with high-risk PCa. It included men who were starting long-term HT for the first time. The trial previously found that docetaxel improved survival compared to SoC (hazard ratio [HR], 0.78), and that abiraterone acetate with prednisolone (AAP) also improved survival compared to the same SoC (HR, 0.63).

First author Matthew Sydes, statistician, MRC Clinical Trials Unit, University College London, UK, said: "Right now, oncologists and urologists want to know which combination is preferable, which is why we conducted this analysis."

The analysis used prospectively collected data from the STAMPEDE trial to directly compare men randomised to the docetaxel and AAP arms while both arms of the trial were recruiting. Randomisations overlapped between November 2011 and March 2013. This comparison included 566 men, of whom 189 were randomised to receive docetaxel and 377 were randomised to receive AAP, both on top of SoC androgen-deprivation

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Reduced Dose Cabazitaxel After Docetaxel in Metastatic Castration-Resistant Prostate Cancer

In the phase III PROSELICA trial reported by Eisenberger et al. in the *Journal of Clinical Oncology*, a cabazitaxel dose of 20 mg/m² (C20) was noninferior for overall survival vs. currently recommended dose of 25 mg/m² (C25) after docetaxel therapy in metastatic castration-resistant prostate cancer (mCRPC). Both doses were recommended for phase II and III testing, and there was evidence the lower dose was associated with less toxicity.

In the open-label trial, 1,200 men from 172 sites in 22 countries were randomized to receive C20 (n=598) or C25 (n=602) plus prednisone 10 mg/day. Median overall survival was 13.4 months in the C20 group vs. 14.5 months in the C25 group (Hazard ratio [HR] 1.024; the upper bound-

ary of the HR confidence interval [CI] (1.184) met the noninferiority margin). Median progression-free survival was 2.9 vs. 3.5 months (HR 1.1, 95% CI 0.97-1.24). The C25 group had better overall survival vs. currently recommended dose of 25 mg/m² (C25) after docetaxel therapy in metastatic castration-resistant prostate cancer (mCRPC). Both doses were recommended for phase II and III testing, and there was evidence the lower dose was associated with less toxicity.

Common side effects of any grade were diarrhea (30.7 vs. 39.8% in the C20 and C25 groups, respectively), fatigue (24.7 vs. 27.1%), and hematuria (14.1 vs. 20.8%). Grade ≥3 adverse events occurred in 39.7 vs. 54.5%, with the most common being fatigue (2.6%) and febrile neutropenia (2.1%) in the C20 group and febrile neutropenia (9.2%) and hematuria (4.2%) in the C25 group. Grade ≥3 hematologic abnor-

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Health-Related Quality of Life for Immediate vs. Delayed Androgen Deprivation Therapy in Patients with Asymptomatic, Non-Curable Prostate Cancer (TROG 03.06 and VCOG PR 01-03 [TOAD]): A Randomised, Multicentre, Non-Blinded, Phase 3 Trial

Duchesne GM, Woo HH, King M, et al.

Lancet Oncol 28 July 2017 [Epub ahead of print]

Background: Androgen-deprivation therapy (ADT) in patients with prostate cancer who have relapsed with rising PSA concentration only (PSA-only relapse), or with non-curable but asymptomatic disease at diagnosis, could adversely affect quality of life (QoL) at a time when the disease itself does not. We aimed to compare the effect of immediate versus delayed ADT on health-related QoL over five years in men enrolled in the TOAD (Timing of Androgen Deprivation) trial.

Methods: This randomised, multicentre, open-label, phase 3 trial done in 29 public and private cancer centres across Australia, New Zealand, and Canada compared immediate with delayed ADT in men with PSA-only relapse after definitive treatment, or de-novo non-curable disease. Patients were randomly assigned (1:1) with a database-embedded, dynamically-balanced algorithm to immediate ADT (I-ADT, immediate therapy group) or to delayed ADT (D-ADT, delayed therapy group). Any type of ADT was permitted, as were intermittent or continuous schedules. The European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaires QLQ-C30 and PR25 were completed before randomisation, every six months for two years, and annually for a further three years. The primary outcome of the trial, reported previously, was overall survival, with global health-related QoL at two years as a secondary endpoint. Here we report prespecified secondary

objectives of the QoL endpoint. Analysis was by intention to treat. Statistical significance was set at $p=0.0036$. The trial was registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12606000301561, and ClinicalTrials.gov, number NCT00110162.

Findings: Between Sept 3, 2004, and July 13, 2012, 293 men were recruited and randomly assigned; 151 to the D-ADT group and 142 to the I-ADT group. There was no difference between the two groups in global health-related QoL over two years from randomisation. There were no statistically significant differences in global QoL, physical functioning, role functioning, or emotional functioning, fatigue, dyspnea, insomnia, or feeling less masculine over the entire five years after randomisation. Sexual activity was lower in the I-ADT group than in the D-ADT group at six and 12 months (at six months mean score 29.20 [95% confidence interval (CI) 24.59-33.80] in the D-ADT group vs. 10.40 [6.87-3.93] in the I-ADT group, difference 18.80 [95% CI 13.00-24.59], $p<0.0001$; at 12 months 28.63 [24.07-33.18] vs. 13.76 [9.94-17.59], 14.86 [8.95-20.78], $p<0.0001$), with the differences exceeding the clinically significant threshold of 10 points until beyond two years. The I-ADT group also had more hormone-treatment-related symptoms at six and 12 months (at six months mean score 8.48 [95% CI 6.89-10.07] in the D-ADT group vs. 15.97 [13.92-

18.02] in the I-ADT group, difference -7.49 [-10.06 to -4.93], $p<0.0001$; at 12 months 9.32 [7.59-11.05] vs. 17.07 [14.75-19.39], -7.75 [-10.62 to -4.89], $p<0.0001$), but with differences below the threshold of clinical significance. For the individual symptoms, hot flushes were clinically significantly higher in the I-ADT group (adjusted proportion 0.31 for D-ADT vs. 0.55 for I-ADT, adjusted odds ratio 2.87 [1.96-4.21], $p<0.0001$) over the five-year period, as were nipple or breast symptoms (0.06 vs. 0.14, 2.64 [1.61-4.34], $p=0.00013$).

Interpretation: Immediate use of ADT was associated with early detriments in specific hormone-treatment-related symptoms, but with no other demonstrable effect on overall functioning or health-related QoL. This evidence can be used to help decision making about treatment initiation for men at this disease stage.

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Doc Moyad's What Works & What is Worthless or "No Bogus Science" Column

"Umm, so it is okay to do PSA screening but what about lifestyle changes?!"

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.

"After differences in implementation and settings are accounted for, the ERSPC and PLCO provide compatible evidence that screening reduces prostate cancer (PCa) mortality." This was the latest published quotation. So now it is okay to do some prostate cancer screening, but why not also use the data to push lifestyle changes and preventive medicine?

First the task force tells us that we should not screen based primarily on the evidence from two major clinical trials known as "ERSPC" and "PLCO." And, recently a bunch of fabulous experts got together, reanalyzed the research and came up with the conclusion that PCa screening does indeed appear to reduce the risk of dying from PCa! YEAH!!! So, obviously now PSA screening recommendations will change from do not screen to screen some individuals that could benefit from PSA screening! YEAH!!! Still, what never seems to change is the additional story that does not get attention when disease screening is endorsed.

What is that story? It is the bigger picture of life and life expectancy. This most recent publication endorses some type of screening and evaluates the evidence from the ERSPC and PLCO trials.

In ERSPC, there were 13,652 overall deaths in the group that was screened and 299 of those deaths were from PCa, which means 2.2% of the deaths in the PSA screened group were from PCa and 97.8% of the deaths were from other causes. And, in the PLCO study there were

6,940 deaths and 152 were from PCa, which means again 2.2% of the deaths in the PSA screened group were from PCa and, again, 97.8% of the deaths were from other causes. Amazingly, both US and European studies showed the EXACT same percentage of deaths due to PCa in the groups that were screened!

Okay, so what does this mean Moyad? What it means is that PSA screening is important, but also that overall preventive care and trying to reduce your risk of dying from other causes are also just as important because almost 98% of men in the PSA screening study are still dying from other causes. This is why it is not only important to screen for PSA in the right men but also to selectively screen for other medical conditions (in men and in women). In an at-

ESMO: Equal Benefit from Two New Treatments

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therapy (ADT), with radiotherapy (RT) for some men.

The estimate for the primary outcome of overall survival was an HR of 1.16, and the difference between the two treatments was not statistically significant, with confidence intervals (Cis) capturing estimates favouring both AAP and docetaxel.

For early outcome measures of failure-free survival and progression-free survival, estimates of treatment effect clearly favoured AAP with HRs of 0.51 and 0.65, respectively. The estimates of treatment effect for late outcome measures of freedom from

tempt to live longer and better, reducing your risk of dying young from all causes is as important as reducing the risk of dying from PCa. And, this does not appear to get as much attention in the debate over screening.

In other words, for many of you reading this column, exercise, not smoking, reducing excessive sun exposure, drinking in moderation or not at all, weight loss, normal blood sugar and cholesterol, normal blood pressure, good diet, preventive vaccines, reducing stress, anxiety and depression – matter as much as PSA screening! This is part of the legacy of ERSPC and PLCO that always needs more news and overall attention. Now, I will step off my rather large soap box my friends!

References:

1. Tsodikov A, Heijnsdijk E, Gulati R, et al. *Ann Intern Med* 5 Sept 2017 [Epub]

metastatic progression and freedom from symptomatic skeletal events favoured AAP, but the differences between treatment groups were not statistically significant.

Sydes said: "This comparison was underpowered, but it is the only data we have to directly compare docetaxel and AAD in this setting."

Professor Nicholas D. James, Chief Investigator of STAMPEDE and Consultant Oncologist at University of Birmingham and Queen Elizabeth Hospital, Birmingham, UK,

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A Critical Comparison of Techniques for MRI-Targeted Biopsy of the Prostate

MRI-targeted biopsy is a promising technique that offers an improved detection of clinically significant prostate cancer over standard non-targeted biopsy. It is established that prostate MRI is of use in both the primary and repeat biopsy setting for the detection of significant prostate cancer.

There are three approaches to targeting biopsies to areas of interest seen on prostate MRI. They each rely on the acquisition and reporting of a diagnostic quality multi-parametric MRI scan used to identify areas of interest, and the subsequent use of those diagnostic quality images in combination with real-time images of the prostate during the biopsy procedure.

The three techniques are:

- Visual registration of the MRI images with a real-time ultrasound image;
- Software-assisted fusion of MRI images and real-time ultrasound images, and
- In-bore biopsy, which requires registration of a diagnostic quality MRI scan with a real time interventional MRI image.

In this paper we compare the three techniques and evaluate those studies where there is a direct comparison of more than one MRI-targeting technique. PubMed was searched from inception to November 2016 using the search terms (cognitive registration OR visual registration OR fusion biopsy OR in-bore biopsy OR targeted biopsy) AND (prostate cancer OR prostate adenocarcinoma OR prostate carcinoma OR prostatic carcinoma OR prostatic adenocarcinoma)

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African American Men with Low-Risk Prostate Cancer are Candidates for Active Surveillance: The Will-Rogers Effect?

Qi R, Moul J

Am J Men's Health 1 August 2017 [Epub]

It is controversial whether African American men (AAM) with low-risk prostate cancer (PC) should be placed on active surveillance (AS). Recent literature indicates AAM diagnosed with low-risk disease have an increased risk of pathologic upgrading and disease progression.

We evaluated surgical pathology of AAM and Caucasians who underwent radical prostatectomy (RP) to assess the suitability of AAM for AS. We retrospectively reviewed 1,034 consecutive men who underwent open RP between 2004 and 2015; 345 Caucasians and 58 AAM met the AUA criteria for low-risk PC. We excluded from analysis two men whose RPs were aborted. Chi-square test, Fisher's exact test, and Wilcoxon rank sum test were used for statistical analysis.

At RP, AAM with low-risk PC have a lower rate of surgical upgrading vs. Caucasians (29.8% vs. 44.5%, $p < 0.04$), but similar rates of adverse pathology. However, AAM overall were less likely to be clinically diagnosed with low-risk cancer (33.1 vs. 41.7%, $p < 0.05$). AAM with low-risk pathology were younger (median age 55 vs. 59 years, $p < 0.001$) and had smaller prostates (32 vs. 35 g, $p < 0.04$). AAM with low-risk PC have lower rates of upgrading at RP and similar adverse pathology vs. Caucasians. There may be a "Will-Rogers" effect as AAM with aggressive disease may be more likely stratified into intermediate- and high-risk groups, leaving AAM with low-risk disease fully eligible for AS. Our results support AS as a viable option for AAM.

ADT May Be Associated With Higher Risk of Heart Failure in Early-Stage Prostate Cancer

Men with localized PCa who received ADT were at significantly higher risk of heart failure than men who did not receive this therapy, according to a Kaiser Permanente (KP) study published in the *British Journal of Cancer*.

"In the past, ADT has been used for advanced PCa, but it is increasingly being used to treat localized PCa. However, the safety, risk, and benefits of this therapy have not been established," said lead author Reina Haque, PhD, MPH, a researcher with KP Southern California Department of Research & Evaluation.

The goal of ADT is to reduce levels of androgens in order to stop them from stimulating PCa cells to grow. ADT can lower androgen to the same level as surgical castra-

tion within three weeks. This research, which looked at a large cohort of men with localized PCa, suggests ADT may be related to increased risk of cardiovascular disease (CVD) in this population.

KP researchers followed a cohort of 7,637 men diagnosed with localized PCa between 1998 and 2008 initially under "watchful waiting." Researchers followed them for up to 12 years after diagnosis. Nearly 30% were treated with ADT. Many of the men were under the age of 60.

To determine the effect of ADT on men with localized PCa, researchers assessed a comprehensive set of factors, including preexisting CVD, diabetes, hypertension, use of cardiovascular medi-

Prostate Specific Antigen Testing After Radical Prostatectomy: Can We Stop At 20 Years?

Ludwig WW, Feng Z, Trock BJ, Humphreys E, Walsh PC

J Urol 14 August 2017 [Epub]

This study examines the clinical features and outcomes associated with delayed biochemical recurrence (BCR) after radical prostatectomy (RP), specifically amongst men with over 20 years of follow-up.

16,720 men underwent RP and 2,699 experienced BCR. We determined predictors of delayed BCR as well as metastasis-free survival and cancer-specific survival rates for recurrence at various time points after RP. We performed a subset analysis of the 732 men with 20 or more years of recurrence-free follow-up. Cumulative incidence curves for metastasis and prostate cancer death were calculated and stratified by BCR time-points.

Predictors of delayed BCR included elevated PSA at the time of RP, higher clinical and

pathologic stage and positive surgical margins. Delayed BCR was associated with favorable cumulative incidence curves for metastasis and prostate cancer death compared to early BCR.

Amongst the 732 men with an undetectable PSA at 20 years, 17 (2.3%) developed a BCR, a single patient developed metastatic disease, and none died due to prostate cancer. The actuarial probability of BCR amongst men with an undetectable PSA at 20 years increased with adverse pathologic features.

Men with delayed BCR have favorable clinical features and improved survival. Men with an undetectable PSA 20 years after RP had a very low rate of recurrence and no deaths due to prostate cancer. This suggests 20 years is a reasonable time to discontinue PSA testing.

cations, smoking, body mass index, and PSA levels. This allowed the researchers to account for the differences that could increase the risk of heart attacks, such as smoking or previous CVD.

The study found that for men with localized PCa, ADT was associated with:

An 81% increased risk of heart failure in men without preexisting CVD;

A 44% increased risk of heart rhythm (arrhythmias) for men with preexisting CVD;

A three-time higher risk for men with preexisting CVD of developing conduction disorder (interruption of the electrical impulses to the heart).

"The implication is that men with localized PCa should be followed to minimize the

health effects of ADT on the cardiovascular system," Dr. Haque said. "Men should consider lifestyle changes and physicians should actively monitor patient health for early signs of heart disease."

"The findings allow men with localized PCa to consider the positive and negative effects of ADT and discuss it with their physicians," continued Dr. Haque. "If they move forward with the therapy, men should work with their physicians to adjust lifestyle to reduce the risk of CVD."

The content in this post has not been reviewed by the American Society of Clinical Oncology, Inc. (ASCO®) and does not necessarily reflect the opinions of ASCO.

The ASCO Post
31 August 2017

Critical Comparison

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AND (MRI OR NMR OR magnetic resonance imaging OR mpMRI OR multiparametric MRI). The initial search included 731 abstracts.

Eleven full text papers directly compared two or more techniques of MRI-targeting, and were selected for inclusion. The detection of clinically significant prostate cancer varied from 0% to 93.3% for visual registration, 23.2% to 100% for software-assisted registration and 29% to 80% for in-bore biopsy.

Detection rates for clinically significant cancer are dependent on the prevalence of cancer within the population biopsied which, in turn, is determined by the selection criteria (biopsy naïve, previous negative biopsy, PSA selection criteria, and presence of a lesion on MRI). Cancer detection rates varied more between study populations than between biopsy approaches. Currently, there is no consensus on which type of MRI-targeted biopsy performs better in a given setting. Although there are studies supporting each of the techniques, substantial differences in methodology and reporting the findings make it difficult to reliably compare their outcomes.

Medscape Oncology
31 August 2017

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Bone Health and Bone-Targeted Therapies for Non-Metastatic Prostate Cancer: A Systematic Review and Meta-Analysis

Alibhai SMH, Zukotynski K, Walker-Dilks C, et al.

Ann Intern Med 167: 341-350, 2017

Background: Bone health is a significant concern in men with prostate cancer.

Purpose: To evaluate the effectiveness of drug, supplement, and lifestyle interventions aimed at preventing fracture, improving bone mineral density (BMD), or preventing or delaying osteoporosis in men with nonmetastatic prostate cancer.

Data Sources: Ovid MEDLINE (1946 to 19 January 2017), EMBASE (1980 to 18 January 2017), and the Cochrane Database of Systematic Reviews (19 January 2017).

Study Selection: Randomized trials and systematic reviews of trials that were published in English; involved men with nonmetastatic prostate cancer; and compared bone-

targeted therapies with placebo, usual care, or other active treatments.

Data Extraction: Two reviewers independently extracted study characteristics and assessed study risk of bias for each outcome.

Data Synthesis: Two systematic reviews and 28 reports of 27 trials met inclusion criteria. All trials focused on men with nonmetastatic prostate cancer who were initiating or continuing androgen deprivation therapy (ADT). Bisphosphonates were effective in increasing BMD, but no trial was sufficiently powered to detect reduction in fractures. Denosumab improved BMD and reduced the incidence of new radiographic vertebral fractures in one high-quality trial. No

trials compared calcium or vitamin D versus placebo. Three lifestyle intervention trials did not show a statistically significant difference in change in BMD between exercise and usual care.

Limitations: Most trials were of moderate quality. Only two randomized controlled trials were designed to examine fracture outcomes. Potential harms of treatments were not evaluated.

Conclusion: Both bisphosphonates and denosumab improve BMD in men with nonmetastatic prostate cancer who are receiving ADT. Denosumab also reduces risk for radiographic vertebral fractures, based on one trial. More trials studying fracture outcomes are needed in this population.

Long-Term Follow Up of a Matched Cohort Study Evaluating the Role of Adjuvant Radiotherapy for Organ-Confining Prostate Cancer with a Positive Surgical Margin

Bhindi B, Carlson RE, Mason RJ, et al.

Urology 17 August 2017 [Epub]

This study evaluates whether adjuvant radiotherapy (aRT, *adjuvant RT to the prostate fossa*) is associated with improved long-term oncologic outcomes for pT2NOR1 prostate cancer.

Men with pT2N0 prostate cancer (*pathological stage 2 with no lymph node metastases*) and a single positive surgical margin following radical prostatectomy and pelvic lymphadenectomy were identified (1987-1996). Men who received aRT were matched 1:1 to men who did not receive aRT based on age, year of surgery, Gleason score, pre-operative PSA, site of PSM, and DNA ploidy. Biochemical recurrence, local

recurrence, distant metastasis, and overall survival were compared between groups in time-to-event analyses.

The cohort included 152 men (76 per group) with a median 20-year follow-up (interquartile range [IQR] 19.2). ART was associated with a lower cumulative incidence of biochemical recurrence (25 vs. 52%; $p < 0.001$) and local recurrence (3 vs. 12%; $p = 0.03$), but no significant differences in cumulative incidence of distant metastasis (10% vs. 7%; $p = 0.44$) or in probability of OS (56 vs. 68%; $p = 0.08$) at 20 years. In competing risks models, receipt of aRT was associated with reduced risks of biochemical recurrence

(hazard ratio [HR], 0.40; 95% confidence interval [CI] 0.23-0.70; $p < 0.001$) and local recurrence (HR, 0.21, 0.05-0.98; $p = 0.05$) but not distant metastasis (HR, 1.56, 0.51-4.75; $p = 0.43$). In the Cox model, aRT was not associated with improved survival (HR=1.56, 0.94-2.57; $p = 0.08$).

ART was associated with reduced risks of biochemical recurrence and local recurrence for men with pT2NOR1 prostate cancer. However, aRT was not significantly associated with metastasis-free or overall survival benefits, as recurrences in these patients generally followed an indolent trajectory with 20-years of median follow-up.

The Effect of Radical Prostatectomy, External Beam Radiation Therapy and Active Surveillance on Life Insurance Premiums in Patients with Prostate Cancer

Piecuch M, Biebel M, Stock J, et al.

Urology Practice 4: 373-377, 2017

Introduction: Men with early-stage, low-risk prostate cancer (PCa) are typically treated with radical prostatectomy (RP), external beam radiation therapy (EBRT) or active surveillance (AS). We examine how these different management options affect life insurance underwriting practices.

Methods: A total of 20 life insurance companies were sent questionnaires with

nine sample patient cases. Men were diagnosed with low-risk PCa at age 55, 65 or 75 years, and treated with RP, EBRT or AS. The life insurance companies were then asked what their underwriting decision would be (standard, substandard or decline) for each sample patient if he submitted a \$500,000 term life insurance application at one, three and five years after treatment

initiation with no evidence of disease on followup.

Results: Of the 20 life insurance companies 12 (60%) responded to the questionnaire. In all age groups, standard life insurance premiums were most likely to be granted after RP (52.7%), followed by EBRT (36.0%) and lastly by AS (5.6%). Regardless of management option, standard premiums were also more likely to be granted if PCa was diagnosed

at an older age and if there was longer duration of disease-free follow-up (54.6% after five years vs. 31.0% after one year).

Conclusions: For men diagnosed with low-risk PCa, life insurance companies are more likely to grant standard life insurance premiums after RP or EBRT rather than AS. Other predictors of favorable decisions are older age at diagnosis and longer duration of disease-free follow-up.

New Look at Old Data Confirms Mortality Benefit from PSA Screening

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for men about screening – upgrading those recommendations to a grade of C.

Otis Brawley, MD, Chief Medical Officer of the American Cancer Society (ACS) who was not involved in the research, said that this data “truly supports” what the ACS has been saying since 2010 – that the decision to screen should be made after an informed discussion between doctor and patient. “Within the physician/patient relationship – not in a mall, at the state fair, or at the 1996 Republican National Convention – there should be a discussion about potential benefits and harms of PCa screening,” he said.

But these recommendations “relied heavily” on results from the ERSPC and the PLCO, said the authors – studies with conflicting results. The ERSPC found a 21% reduction in mortality rates, but the PLCO found “no difference” in mortality.

However, Tsodikov and colleagues argued that differences in the trial results were “complicated by differences in their implementation.” The PLCO was conducted in the

U.S., where PCa incidence is higher than in Europe, in a U.S. practice-based setting, where the control group likely had more frequent screening than in the ERSPC control group,” they said. In addition, PLCO compared “organized screening vs. opportunistic screening” as opposed to screening vs. no screening, and age ranges were slightly different (ERSPC examined men ages 55 to 69, while PLCO examined men ages 55 to 74 years). Other methodological differences included:

- Shorter screening interval (annual vs. every two to four years)
- Higher PSA threshold for biopsy referral (4.0 vs. 3.0 µg/L [ng/mL])
- Stopped regular screening after six rounds

Using individual records from both trials, researchers performed extended analyses to account for “screening intensity” by estimating mean lead times. While they found no difference on the effects of screening on mortality between trials (P value 0.37-0.47 for interaction), they did find that a longer mean lead time was linked to a significantly

lower risk of PCa deaths, after adjusting for baseline risks between trial setting and participant age.

Brawley did note that mean lead time is “not a standard measure we use in epidemiology,” characterizing it as “somewhat controversial.”

An accompanying editorial by Andrew J. Vickers, PhD, of Memorial Sloan Kettering Cancer Center in New York City, compared the ERSPC and the PLCO trials to “a trial of 1,000 mg of aspirin vs. placebo with a trial of 1,000 mg vs. 900 mg of aspirin.”

He added that he hoped this research would help to “refocus” the debate about PSA testing. Vickers called for “commonsense strategies,” such as shared decision making, to stop screening men over 70 and that biopsy should only be done in men “who screen positive and are at risk for aggressive disease. PSA-based screening does reduce PCa mortality, but whether this benefit outweighs the harms of overdiagnosis and overtreatment depends on how screening is implemented,” Vickers wrote.

Brawley, who characterized the editorial as “a must-read for primary care physicians,”

added that more and more men who are diagnosed with PCa through screening are receiving observation as a form of therapy, rather than aggressive radiation. “The risk/benefit ratio is changing because nowadays, nearly half of all men diagnosed through screening are being watched, whereas 10 years ago, almost no one was being watched,” he noted.

*MedPage Today
4 September 2017*

Two New Treatments

(Continued from page 3)

said: “The individual trials suggested that abiraterone may have a larger effect on survival than docetaxel, but this did not translate into a clear advantage in this study.

Both drugs provide a survival advantage over standard of care alone in men with high-risk prostate cancer beginning long-term hormone therapy. This study suggests that starting with either drug is acceptable and choice may depend on availability.

*ESMO 2017 Press Release
8 September 2017*

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, "New Look at Old..."

The debate about screening is back in the news because of a new report that combines both the European and U.S. screening trials. Both trials have important limitations. The European study that showed a survival benefit suffered from differences in management, with more men in the control group treated more conservatively, and the American trial suffered from heavy contamination. This new report attempts to combine data and it concludes that screening does improve overall survival; however, their analysis uses an unusual assessment method.

Regardless of the merits of their findings, the debate again turns back to several caveats. First, don't screen men with little chance of benefitting, such as men with shorter life expectancy. Second, don't aggressively treat the large percentage of men who have a non-life threatening tumor. And third, make sure to discuss the pros and cons with each individual before testing so that a man can participate in the decision; ordering a PSA test without first discussing it with a patient is not in anyone's best interest.

The Bottom Line: Combined analysis of two randomized studies suggests screening lowers mortality, but the power of this conclusion is limited from problems in each study. Men should participate in the joint decision to undergo PSA testing.

P1, "Reduced Dose..."

Although chemotherapy agents are able to kill many cancer cells, they all have the potential to cause side ef-

fects. Choosing the best dose is based on choosing one that is both effective and well tolerated. Research studies often try to determine the lowest dose that can be given to improve survival while minimizing side effects. The study by Eisenberg et al. tested two doses of cabazitaxel and found that the lower dose of 20 mg/m² had a similar survival as the standard dose of 25 mg/m², but it did cause fewer side effects. Although the dose of 25 mg/m² is the usual recommended dose, the guidelines do include a recommendation to reduce it to 20 mg/m² if serious side effects occur. This study should encourage doctors to start with the lower dose to minimize side effects without being concerned about compromising the improvement in survival.

The Bottom Line: Based on non-inferiority of the dose of 20 mg/m² of cabazitaxel, doctors should consider it when starting a patient with metastatic castrate resistant disease on this treatment.

P4, "African American..."

Should African-American men (AAM) with low-risk disease be managed with active surveillance? That question has not been resolved but some clinicians have suggested that it is a bad idea because of the possible greater potential for undergrading the disease. The study by Moul provides added support for still offering AS to AAM. In a retrospective analysis they found that Caucasians were significantly more likely to have upstaging than AAM. Although this study is supportive, it is not definitive. What

is missing is information about the men with low-risk localized disease who were not managed conservatively for both Caucasians and AAM. It is possible that some unknown selection bias did occur. Greater confidence in these findings might be possible if two consecutive cohorts of men were all managed in a similar fashion. That would reduce the selection bias, although such a study would be quite difficult to perform.

The Bottom Line: This uncontrolled study suggests that AAM are not at increased risk for upgrading of their disease and therefore remain good candidates for AS, although the study is not definitive.

P4, "PSA Testing After..."

Do all men treated by radical prostatectomy (RP) need permanent monitoring or can it be discontinued after a set number of years. Ludwig et al. address this question by reviewing a cohort of men followed for more than 20 years. Although the recurrence was higher for men with higher pathological stage, overall, only 2.3% of men developed a rising PSA beyond 20 years after surgery and none died of their disease. One caution, however, is we do not know how long these men were followed beyond the 20 year mark. Based on their findings, they suggest that 20 years is a sufficient time at which PSA monitoring can be stopped.

The Bottom Line: Twenty years may be a sufficient time period beyond which PSA monitoring is no longer necessary after RP.

P4, "ADT May Be ..."

Doctors have become increasingly aware of the potential side effects of ADT. For men with advanced disease, the trade offs are a necessary consequence where, in most cases, the benefits outweigh the risks. But that may be less true for men with localized disease, where the benefits of therapy are less certain. Hague et al. conducted an analysis of men with localized disease who were initially treated by conservative therapy and over time may have received ADT. They found that even in men with no cardiovascular disease, there was an 81% higher risk of heart failure when men were followed for 12 years. In men with known cardiovascular disease, heart rhythm problems were also much more common in those men receiving ADT. Although not based on randomized studies, these findings suggest that careful evaluation is needed when men that have non-metastatic disease with a long life expectancy are placed on ADT.

The Bottom Line: ADT appears to have cardiovascular risks even in men with no history of cardiovascular disease, which means careful monitoring is needed when it is given to men with non-metastatic disease.

P5, Long-Term Follow-up..."

Should a man with a positive margin after RP receive adjuvant radiation therapy (RT)? Data from randomized studies show improvement in biochemical recurrence (BCR) and in some cases, metastases; however, it is unclear if survival is improved. The study by Bhindi et al. provides

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Cabazitaxel Dosage

(Continued from page 1)

malities included neutropenia and leukopenia. Serious adverse events occurred in 30.5 vs. 43.2%, and possible treatment-related events resulted in discontinuation in 16.4 vs. 19.5%. Health-related quality of life did not differ between the groups.

Investigators concluded: "Efficacy of cabazitaxel in mCRPC patients post-docetaxel was confirmed. The noninferiority end point was met.... Secondary efficacy end points favored C25. Fewer adverse events were observed with C20."

The ASCO Post, 24 August 2017

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

additional data from an uncontrolled trial showing again that BCR and local recurrence are reduced; however, in this study neither metastases nor survival was improved. The ongoing debate is whether it is worth offering adjuvant treatment to all men or to wait until a BCR develops and then offer RT at that time. Waiting spares many men from a treatment that will not help their overall survival and may miss out on helping only a small number of men.

The Bottom Line: Adjuvant RT appears to reduce BCR but may not really improve overall survival.

P6, "The Effect of Radical..."

Pieceuch et al. conducted an interesting study about the theoretical behavior of insurance companies when a patient has been diagnosed with localized prostate cancer. Of the companies responding, a standard policy would more likely be granted to a man treated by RP, followed by a man treated by RT and least likely to a man treated by AS. This occurred for all ages presented in this hypothetical analysis. These findings are very concerning. First, no randomized data have demonstrated improved outcomes for men treated by surgery and for men

with Gleason 6 cancer and there are is no clear inferiority of AS compared to the other two options. Based on this survey, some communication is needed between the AUA and the insurance companies that responded to review the existing data and hopefully have them change their policy to reflect the current data available.

The Bottom Line: Insurance companies need to address their apparent disparity between the men they would insure based on the treatment a patient receives to reflect current knowledge.

Clark Atlanta Awarded \$1.5 Million Prostate Cancer Grant

Clark Atlanta University

The Center for Cancer Research and Therapeutic Development (CCRTD) at Clark Atlanta University, together with the University of Texas at El Paso (UTEP) and Vancouver Prostate Centre, has been awarded a \$1.5 million grant by the Department of Defense Prostate Cancer Research Program to develop groundbreaking drugs to aid in the treatment of castration-resistant prostate cancer, the deadliest form of the disease.

Dr. Jaideep Chaudhary, professor in the Department of Biological Sciences and interim associate dean, School of Arts and Sciences, will be the principal investigator for CAU. Dr. Chaudhary will conduct preclinical trials of newly designed drugs emanating from this collaborative research project.

"This grant is extremely significant for the Cancer Center as it addresses our mission of developing treatments for prostate cancer, which disproportionately affects African American men," said Chaudhary.

As of 2013, the most recent year for which statistics exist, Black men had the highest rate of contracting prostate cancer, according to the Centers for Disease Control and Prevention. The CDC also found in the same year Blacks have a higher death rate from prostate cancer than other ethnic groups.

CCRTD is one of the leading cancer research centers in the nation focused solely on treating and eliminating prostate cancer in Black men. The Center was established at CAU in 1999 through combining the joint strengths of the Departments of Biological Sciences and Chemistry. It has strategic partnerships with colleges, universities and laboratories worldwide, including Emory University, Morehouse College, Cornell University and iThemba LABS in South Africa.

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