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# Hot SHEET

**Us TOO INTERNATIONAL** Prostate Cancer Education and Support Network

## First Results for Nanosphere Focal Therapy in Prostate Cancer

When imaging of the prostate shows only one small area of cancer, "why can't you treat just that spot, instead of the whole prostate?" frustrated patients keep asking. "This is what a new approach now being tested aims to do," says Ardeshir R. Rastinehad, DO, director of focal therapy and interventional urologic oncology at the Icahn School of Medicine at Mount Sinai, New York City.

His team has just reported early results from a small trial of focal therapy for discrete lesions in the prostate using gold-silica nanoshell (GSN)-directed laser technology (also called AuroLase Therapy, developed by Nanospectra). The study was conducted in 15 men who had low- to intermediate-risk prostate cancer. There were no serious side effects after 90 days, which was the primary endpoint of the study. At 12

months, 87.5% of the lesions tested negative for tumor in the ablation zone. "This current pilot device study demonstrates that GSN-directed laser excitation and ablation is a safe and technically feasible procedure for the targeted destruction of prostate cancer," the study authors conclude. The study was published online August 26 in the *Proceedings of the National* (Continued on page 4)

## Second Generation Antiandrogens Carry Heart Risks

**Men with Three or More Cardiac Comorbidities had Highest Risk of Premature Death within Six Months**

The goal of this study was to investigate the short-term safety outcomes of the second-generation antiandrogens abiraterone acetate (AA) or enzalutamide (ENZ) in elderly prostate cancer patients with pre-existing cardiovascular diseases (CVDs).

Men with advanced prostate cancer who had a history of CVDs had an increased risk of early death at six months when treated with the oral androgen signaling inhibitors AA or ENZ, according to a population-based retrospective study.

In a study of men 65 years or older, those who had three or more cardiac conditions had an increased risk of all-cause mortality at six months with these drugs (relative risk [RR] 1.56, 95% CI 1.29-1.88) compared with men without a history of CVDs, and this greater risk was seen in both the pre- and post-chemotherapy setting, reported Grace Lu-Yao, PhD, MPH, of the Sidney Kimmel Cancer Center at Thomas Jefferson University in Philadelphia, and colleagues in *European Urology*. About 67% of men in the study had one or more pre-existing CVD conditions.

Using Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data, LuYao's group found that with AA in the post-chemotherapy setting, 24% of patients in the database had died within the first six months, vs. 17% in the drug's pivotal trial. With ENZ, these rates were 28% vs. 12%, respectively.

Researchers included 2,845 older prostate cancer patients (Continued on page 6)

## Largest Real-World Study of Immunotherapy Shows Men with Advanced Prostate Cancer with Low PSA had a Median Survival of Nearly Four Years After Treatment with PROVENGE® (sipuleucel-T)

Higano CS, Armstrong AJ, Sartor AO, et al.

**Cancer 4 September 2019; Epub ahead of print**

The large cancer registry, PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data (PROCEED) (NCT01306890), evaluated sipuleucel-T immunotherapy for asymptomatic/minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC).

PROCEED enrolled men with mCRPC receiving three bi-weekly sipuleucel-T infusions. Assessments included overall survival (OS), serious adverse events (SAEs), cerebrovascular events (CVEs), and anticancer interventions (ACIs). Follow-up was for ≥three years or until

death or study withdrawal. In 2011-2017, 1,976 men were followed for 46.6 months (median). The median age was 72 years, and the baseline median PSA level was 15.0 ng/mL; 86.7% were white and 11.6% were African American. Among the patients, 1,902 had one or more sipuleucel-T infusions. The median OS was 30.7 months (95% confidence interval [CI], 28.6-32.2 months). Known prognostic factors were independently associated with OS in a multi-variable analysis. Among the 1,255 men who died, 964

(Continued on page 6)

This Issue of the Us TOO Prostate Cancer *Hot SHEET* is made possible by charitable contributions from



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## ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy with Enzalutamide or Placebo in Men with Metastatic Hormone-Sensitive Prostate Cancer

Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al.

J Clin Oncol 22 July 2019; Published early online

**Purpose:** Enzalutamide, a potent androgen-receptor inhibitor, has demonstrated significant benefits in metastatic and nonmetastatic castration-resistant prostate cancer (CRPC). We evaluated the efficacy and safety of enzalutamide in metastatic hormone-sensitive prostate cancer (mHSPC).

**Methods:** ARCHES (ClinicalTrials.gov identifier: NCT02677896) is a multinational, double-blind, phase III trial, wherein 1,150 men with mHSPC were randomly assigned 1:1 to enzalutamide (160 mg/day) or placebo, plus androgen deprivation therapy (ADT), stratified by disease volume and prior docetaxel chemotherapy. The primary end point was radiographic progression-

free survival (rPFS).

**Results:** As of October 14, 2018, the risk of radiographic progression or death was significantly reduced with enzalutamide plus ADT vs. placebo plus ADT (hazard ratio, 0.39; 95% CI, 0.30 to 0.50;  $P < 0.001$ ; median not reached vs. 19.0 months). Similar significant improvements in rPFS were reported in prespecified subgroups on the basis of disease volume and prior docetaxel therapy. Enzalutamide plus ADT significantly reduced the risk of PSA progression, initiation of new antineoplastic therapy, first symptomatic skeletal event, castration resistance, and reduced risk of pain progression. More men achieved an undetectable PSA level and/or an objective response

with enzalutamide plus ADT ( $P < 0.001$ ). Men in both treatment groups reported a high baseline level of quality of life, which was maintained over time. Grade 3 or greater adverse events were reported in 24.3% of men receiving enzalutamide plus ADT vs. 25.6% of those who received placebo plus ADT, with no unexpected adverse events.

**Conclusion:** Enzalutamide with ADT significantly reduced the risk of metastatic progression or death over time vs. placebo plus ADT in men with mHSPC, including those with low-volume disease and/or prior docetaxel, with a safety analysis that seems consistent with the safety profile of enzalutamide in previous clinical trials in CRPC.

## Salvage Radical Prostatectomy for Recurrent Prostate Cancer: Morbidity and Functional Outcomes from a Large Multicenter Series of Open Versus Robotic Approaches

Gontero P, Marra G, Alessio P, et al.

J Urol 202; 725-731, 2019

**Purpose:** Salvage radical prostatectomy (sRP) has historically yielded a poor functional outcome and a high complication rate. However, recent reports of robotic sRP have demonstrated improved results. In this study we assessed sRP functional outcomes and complications when comparing robotic and open approaches.

**Materials and Methods:** We retrospectively collected data on sRP for recurrent prostate cancer after local non-surgical treatment at 18 tertiary referral centers from 2000 to 2016. The Clavien-Dindo classification was applied to classify complications. Complications and

functional outcomes were evaluated by univariable and multivariable analysis.

**Results:** We included 395 sRPs, of which 186 were open and 209 were robotic. Robotic sRP yielded lower blood loss and a shorter hospital stay (each  $p < 0.0001$ ). No significant difference emerged in the incidence of major and overall complications (10.1%,  $p = 0.16$ , and 34.9%,  $p = 0.67$ ), including an overall low risk of rectal injury and fistula (1.58% and 2.02%, respectively). However, anastomotic stricture was more frequent for open sRP (16.57% vs. 7.66%,  $p < 0.01$ ). Overall 24.6% of men had had severe incontinence,

defined as three or more pads per day, for 12 or six months. On multivariable analysis, robotic sRP was an independent predictor of continence preservation (OR 0.411, 95% CI 0.232–0.727,  $p = 0.022$ ). Limitations include a retrospective study design and the absence of a standardized surgical technique.

**Conclusions:** In this contemporary series, to our knowledge, sRP showed a low risk of major complications and better functional outcomes than previously reported. Robotic sRP may reduce anastomotic stricture, blood loss and hospital stay, and improve continence outcomes.

## Doc Moyad's What Works & What is Worthless Column – Also Known as “No Bogus Science” Column

### “Boring B12 Testing & Vacuuming – Part 2?!”

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.

Last month we discussed the boring and low-cost vitamin B12 blood test. This month we will discuss another unsung hero and that is vacuuming! The vacuum is symbolic (aka metaphor) for the greater elimination and depreciation of basic exercise and physical activity around the U.S. Regardless of age, it seems we find more and more ways of reducing physical activity. Mandatory exercise in K through 12<sup>th</sup> grade is basically a thing of the past. As adults we outsource so many activities from removing snow, to cleaning and household chores, and the list is endless. Adults are also more sedentary than ever, partly because technology (computers) requires us to spend more time sitting when accomplishing tasks. I have written almost 150 con-

secutive monthly columns for Us TOO, which means Us TOO has caused me to be sedentary every time I write for them! What to do?

I am convinced there is no better time in American history to revolt against these sedentary habits and try and live somewhat in the past when we had to be physically active to survive in and around the home. Last year I told my wife that I was buying a new handheld and upright vacuum cleaner and, for at least a few times a week, it is Moyad vs. my house! Basement, upstairs, and all the nooks and tight angles and creepy cobwebbed dark spaces in our 1920s home. Total time 60-90 minutes till anything and everything is completely clean, and after each session I am completely exhausted! However, after a

few months I was losing a few pounds, seeing muscles in my abdominal area that abandoned me long ago in the middle of medical school (replaced by pizza & beer). Currently, I am not only obsessed, but addicted to this activity and my wife seems to love me more than ever (vacuuming = aphrodisiac?!).

Now, the latest research from South Korea and my hometown (University of Michigan = Go Blue) on vacuuming suggests it can be considered an “intensive exercise” based on the energy expended!<sup>1</sup> No kidding! Past research from the University of Florida analyzed 17 different household activities and vacuuming and sweeping was at the top of the list in terms of energy expenditure and exercise intensity (similar to rapid walking and

stair climbing)!<sup>2</sup> Researchers actually suggested more of these activities should be prescribed by health care professionals as we age.

Now, I am looking for a push mower for next summer (no kidding) and other ways to improve my exercise level without running 10 miles a day (which I used to do). Again, it is the boring stuff that helps us live better mentally and physically! Throw out your high-end home treadmill, elliptical, or pricey exercise club membership because vacuuming kicks all of that stuff in the gluteus maximus!

#### References:

1. Bak H, D'Souza C, Shin G. *Appl Ergon* 79: 38-44, 2019
2. Knaggs JD, Larkin KA, Manini TM. *J Am Geriatr Soc* 59: 2118-2123, 2011

## Recent Global Patterns in Prostate Cancer Incidence and Mortality Rates

Culp MB, Soergomataram I, Efsthathiou JA, Bray F, Jemal A

**Eur Urol 04 September 2019; Epub ahead of print**

Previous studies have reported significant variation in prostate cancer rates and trends mainly due to differences in detection practices, availability of treatment, and underlying genetic susceptibility.

Our aim is to assess recent worldwide prostate cancer incidence, mortality rates, and trends using up-to-date incidence and mortality data.

We present estimated age-standardized prostate cancer incidence and mortality rates by country and world regions for 2018 based on the GLOBOCAN database. We also examined rates and temporal trends for incidence (44

countries) and mortality (76 countries) based on data series from population-based registries.

The highest estimated incidence rates were found in Australia/New Zealand, Northern America, Western and Northern Europe, and the Caribbean, and the lowest rates were found in South-Central Asia, Northern Africa, and South-Eastern and Eastern Asia.

The highest estimated mortality rates were found in the Caribbean (Barbados, Trinidad and Tobago, and Cuba), Sub-Saharan Africa (South Africa), parts of the former Soviet Union (Lithuania, Esto-

nia, and Latvia), whereas the lowest rates were found in Asia (Thailand and Turkmenistan).

Prostate cancer incidence rates during the most recent five years declined (five countries) or stabilized (35 countries), after increasing for many years; in contrast, rates continued to increase for four countries in Eastern Europe and Asia. During the most recent five data years, mortality rates among the 76 countries examined increased (three countries), remained stable (59 countries), or decreased (14 countries).

As evident from available

data, prostate cancer incidence and mortality rates have been on the decline or have stabilized recently in many countries, with decreases more pronounced in high-income countries. These trends may reflect a decline in PSA testing (incidence) and improvements in treatment (mortality).

We examined recent trends in prostate cancer incidence and mortality rates in 44 and 76 countries, respectively, and found that rates in most countries stabilized or decreased.

## First Results for Nanosphere Focal Therapy in Prostate Cancer *(Continued from page 1)*

Academy of Sciences. Another study is currently in progress. That study, involving 45 men, is assessing efficacy at a 12-month follow-up.

To grant approval of devices, the US Food and Drug Administration (FDA) requires data for 100 patients. This nanoshell technology may therefore be closer to approval than most believe – “Two years, more or less,” Nanospectra’s chief executive officer, David Jorden, MBA, explained.

Accrual for a study involving 65 men will begin in September 2019. Jorden indicated that Nanospectra will be in a position to submit its data to the FDA in early 2021.

“AuroLase Therapy should be commercially available in less than two years,” he said.

“Our study shows that for low- to intermediate-risk prostate cancer, photothermal ablation provides the ability to avoid overtreatment and avoid the deleterious effects of radical treatment options,” Jenson noted.

Approached for comment, Anthony V. D’Amico, MD, PhD, from the Dana-Farber Cancer Institute, Boston, MA, who was not involved in the study, told Medscape Medical News that efficacy needs to be established in future studies in more men with longer follow-up to assess cancer control and toxicity.

Nanoshells comprise a silica core and a gold shell. They measure 150 nm in diameter. They are designed to absorb near-infrared light and convert it to heat. They accumulate at high levels at tumor sites, owing to their leaky vascular architecture. When near-infrared light from a laser is targeted in a pinpoint manner at the lesion, the nanoshells absorb the light.

The tumor then undergoes photothermal heating, resulting in cell death.

Rastinehad explained that healthy tissue is spared. In healthy tissue, the concentration of nanoshells is low, and so only mild, reversible hyperthermia occurs there.

The safety study enrolled 16 men aged 58 to 79 years with low- to intermediate-risk prostate cancer (Gleason score, 4+3 or less).

The patients were diagnosed and underwent staging that employed high-resolution multiparametric MRI (mpMRI). The regions of interest were overlaid on live ultrasound images. These images guided placement of the laser trocar, which houses a laser catheter, so as to deliver near-infrared light in a pinpoint manner at the site of the lesions, thereby heating the nanoshells.

The procedure was carried out in two stages on consecutive days. On the first day, men received an intravenous infusion of 7.5 mL/kg of nanoshells. On the second day, men underwent laser excitation of the nanoshells under general anesthesia.

The median time under anesthesia, which included patient positioning and equipment preparation, was nearly four hours (230 minutes; range: 115-345).

Patients were discharged on the same day after several hours of monitoring and a successful voiding (urinating) trial. Five men required a Foley catheter post ablation.

After 48 to 72 hours, men underwent mpMRI for evaluation of radiologic treatment response at the planned ablation zone. At three and 12 months, the men underwent repeat mpMRI and MR/ultrasound targeted biopsy.

Men were followed for one, three, six, and 12 months for adverse events. Patients’ International Prostate Symptom Score, urinary quality of life, and Sexual Health Inventory for Men score were assessed. The scores at three, six, and 12 months were similar to baseline values.

Fifteen men completed the study. One patient experienced epigastric pain during the nanoshell infusion and did not undergo laser treatment on day two.

At three months (the primary endpoint time point), median prostate volume had decreased by 7 cm<sup>3</sup> (49 cm<sup>3</sup> at baseline), and the median PSA level had decreased by 2.8 ng/mL (6.7 ng/mL at baseline). Decreases in PSA were sustained through 12 months of observation.

No grade 3/4 adverse events occurred during the procedure. Grade 1/2 hematuria was reported for all 15 men at 90 days post ablation.

Two occurrences of residual disease were reported at three months. According to the investigators, these occurrences may have been due to the positioning of the laser catheter. At three and 12 months, residual disease was observed in two men. The investigators attribute this to incomplete treatment resulting from an underestimation of the lesion volume during procedure planning.

“Pretreatment planning is crucial,” Rastinehad said. He pointed out that if the region of interest is not drawn correctly the laser light will miss its target. “Placement of the trocars is important.”

In a comment to Medscape Medical News, D’Amico said, “One issue is that any form of focal ablation (even if mpMRI directed) does not

ensure cure, because mpMRI can miss lesions that are grade 4 and that are <0.5 cm<sup>3</sup> in size, and certainly misses microscopic disease.

“So the question remains as to whether, by missing such disease even in carefully selected men, they are at risk for worse outcomes than if they are treated when and if their PSA subsequently rises,” he added.

Rastinehad emphasized that the objective of focal ablation therapy is to control cancer and reduce the undesirable side effects that men experience with other approaches that are currently in use.

He noted that pinpoint, tumor-specific ablation ensures less inflammation of prostatic tissue so that patients can undergo surgery successfully, if needed. Indeed, one patient in the study has subsequently undergone robotic prostatectomy successfully, Rastinehad said.

The study was sponsored by Nanospectra Biosciences, Inc. Rastinehad is the national principal investigator for the multi-institutional trial of GSN-directed ablation funded by Nanospectra Biosciences, with whom he also consults. Two coauthors co-founded Nanospectra Biosciences and have an equity stake in the company but have indicated that they are not involved with the company’s business or strategic decisions.

*Medscape Medical News*  
28 August 2019

## Phase 1b Trial of Docetaxel, Prednisone and Pazopanib in Men with Metastatic Castration Resistant Prostate Cancer

George DJ, Halabi S, Healy P, Barak I, Winters C, et al.

The Prostate 09 September 2019; Epub ahead of print

Docetaxel-prednisone is a standard of care for men with metastatic castration-resistant prostate cancer (mCRPC), and plasma vascular endothelial growth factor (VEGF) levels are a poor prognostic factor in this population; therefore, we evaluated the combination of docetaxel prednisone with pazopanib, an oral VEGF receptor inhibitor, for safety and preliminary efficacy.

This is a two-site phase 1b Department of Defense (DoD) Prostate Cancer Clinical Trials Consortium trial of docetaxel, prednisone, and

pazopanib once daily and ongoing androgen deprivation therapy and prophylactic pegfilgrastim in men with mCRPC. The primary endpoint was safety and the determination of a maximum tolerated dose (MTD) through a dose-escalation and expansion design; secondary endpoints included progression-free survival (PFS) and overall survival (OS), PSA declines, radiographic responses, and pharmacokinetic and plasma angiokine biomarker analyses. Twenty-five men were treated over six dose levels. Peg-

filgrastim was added to the regimen after myelosuppression (*bone marrow suppression*) limited dose escalation. With pegfilgrastim, our target MTD of docetaxel 75 mg/m<sup>2</sup> every three weeks, prednisone 10 mg daily and pazopanib 800 mg daily was reached. Eleven additional men were accrued at this dose level for a total of 36 patients. Dose-limiting toxicities included neutropenia (*a low white blood cell count*), syncope (*dizziness*), and hypertension. Three deaths attributed to study treatment occurred. The objective re-

sponse rate was 31%; median PFS was 14.1 months (95% confidence interval [CI]: 7.1 and 22.2 months); and OS was 18.6 months (95% CI: 11.8 and 22.2 months).

The combination of docetaxel, prednisone, and pazopanib (with pegfilgrastim) was tolerable at full doses and demonstrated promising efficacy in a relatively poor risk patients with mCRPC. Further development of predictive biomarkers may enrich for men who receive clinical benefit from this regimen.

## Intensity-modulated Fractionated Radiotherapy Vs Stereotactic Body Radiotherapy for Prostate Cancer (PACE-B): Acute Toxicity from an International, Randomised, Open-label, Phase 3, Non-Inferiority Trial

Brand DH, Tree AC, Ostler P, et al.

Lancet Oncology 17 September 2019; E-pub

**Background:** Localised prostate cancer is commonly treated with external-beam radiotherapy (EBRT). Moderate hypofractionation has been shown to be non-inferior to conventional fractionation. Ultrahypofractionated stereotactic body RT would allow shorter treatment courses but could increase acute toxicity compared with conventionally fractionated or moderately hypofractionated RT. We report the acute toxicity findings from a randomised trial of standard-of-care conventionally fractionated or moderately hypofractionated RT vs. five-fraction stereotactic body RT for low-risk to intermediate-risk localised prostate cancer.

**Methods:** PACE is an international, phase 3, open-label, randomised, non-inferiority trial. In PACE-B, eligible men aged 18 years and older, with

WHO performance status 0-2, low-risk or intermediate-risk prostate adenocarcinoma (Gleason 4 + 3 excluded), and scheduled to receive RT were recruited from 37 centres in three countries (UK, Ireland, and Canada). Participants were randomly allocated (1:1) by computerised central randomisation with permuted blocks (size four and six), stratified by center and risk group, to conventionally fractionated or moderately hypofractionated RT (78 Gy in 39 fractions over 7.8 weeks or 62 Gy in 20 fractions over four weeks, respectively) or stereotactic body RT (36.25 Gy in five fractions over one-two weeks). Neither participants nor investigators were masked to allocation. Androgen deprivation was not permitted. The primary endpoint of PACE-B is freedom from biochemical or clinical fail-

ure. The coprimary outcomes for this acute toxicity substudy were worst grade 2 or more severe Radiation Therapy Oncology Group (RTOG) gastrointestinal or genitourinary toxic effects score up to 12 weeks after RT. Analysis was per protocol. This study is registered with ClinicalTrials.gov, NCT01584258. PACE-B recruitment is complete and follow-up is ongoing.

**Findings:** Between Aug 7, 2012, and Jan 4, 2018, we randomly assigned 874 men to conventionally fractionated or moderately hypofractionated RT (n=441) or stereotactic body RT (n=433). 432 (98%) of 441 men allocated to conventionally fractionated or moderately hypofractionated RT and 415 (96%) of 433 men allocated to stereotactic body RT received at least one fraction of allocated treatment.

Worst acute RTOG gastrointestinal toxic effect proportions were as follows: grade 2 or more severe toxic events in 53 (12%) of 432 men in the conventionally fractionated or moderately hypofractionated RT group vs. 43 (10%) of 415 men in the stereotactic body RT group (difference=1.9 percentage points, 95% CI -6.2 to 2.4; p=0.38). Worst acute RTOG genitourinary toxicity proportions were as follows: grade 2 or worse toxicity in 118 (27%) of 432 men in the conventionally fractionated or moderately hypofractionated RT group vs. 96 (23%) of 415 men in the stereotactic body RT group (difference -4.2 percentage points, 95% CI -10.0 to 1.7; p=0.16). No treatment-related deaths occurred.

(Continued on page 8)

## New Prostate Cancer Blood Test Could Reduce Biopsies

A new blood test that looks for circulating tumor cells (CTC) could significantly improve the diagnosis of prostate cancer and avoid unnecessary biopsies and treatments. Combining the new test with PSA results can yield a diagnosis of aggressive prostate cancer that is more than 90% accurate, according to a *Journal of Urology* study.

“This level of accuracy is higher than that of any other biomarker for prostate cancer,” says senior and corresponding study author Dr. Yong-Jie Lu, a professor of molecular oncology at the Barts Cancer Institute of Queen Mary University of London in the UK.

PSA is a protein that the prostate produces. If there is cancer in the prostate, the gland releases more PSA into the blood. Therefore, raised levels of PSA in the blood can be a sign of prostate cancer. However, other prostate conditions, such as inflammation or noncancerous enlargement of the gland, can also raise PSA levels.

So, to confirm the presence of cancer, the individual undergoes a biopsy, an uncomfortable procedure in which the surgeon removes pieces of the prostate and sends them for tissue analysis. A biopsy of the prostate is not only invasive but also risky, with a high chance of bleeding and infection.

Also, biopsy results of most men with raised PSA levels show that they do not have cancer. Even when prostate biopsies do reveal the presence of cancer, in most cases, the tumor is not aggressive and will not be fatal if doctors leave it untreated.

*(Continued on page 8)*

## Second Generation Antiandrogens Carry Heart Risks *(Continued from page 1)*

treated with AA, and 1,031 treated with ENZ from 2011 to 2014. Most men in the chemotherapy-exposed group were treated with AA or ENZ in 2011-2012, when the agents were approved in a later-line setting, while the chemotherapy-naïve group was largely treated with these agents in 2013-2014.

Notably, two-thirds of men had at least one pre-existing CVD, the most common of which was ischemic heart disease (58.5%), followed by chronic heart failure (32.1%), atrial fibrillation (Afib; 18.8%), stroke (13.4%), and acute myocardial infarction (MI; 6.0%). In all, 17.6% of the entire cohort had three or more CV conditions. Other relevant comorbidities included hypertension in at least 80% of the men and diabetes in about 40%.

Of the 3,876 men, 69.0% had localized or regional disease, and about one-fourth (24.3%) had metastatic disease – others were unknown. “An increased risk of early death was also observed in men with one or two CV conditions, though to a lesser degree (relative risk [RR] 1.16, 95% confidence interval [CI] 1.00-1.36),” they wrote.

Clinical trials typically exclude patients with significant medical problems, but trials for prostate cancer drugs may often include men with uncontrolled hypertension, or a history of major heart conditions such as severe angina (chest pain), heart failure, or a recent MI.

“In the pivotal trial, they usually try to stick with patients who are healthy, but once it’s approved, they’re pretty much used for everyone,” Lu-Yao told MedPage Today.

Lu-Yao and colleagues also examined risk of hospitalizations by looking at hospital

use in the six months before and after starting AA or ENZ. In men already treated with chemotherapy, those with one or two cardiac conditions on either drug had a higher risk of hospitalization compared with those without (incidence rate ratio [IRR] 1.43, 95% CI 1.15-1.78).

In the post-chemotherapy setting alone, neither agent was significantly associated with increased hospitalizations. But in the chemotherapy-naïve AA group, there were significant increases in the risk of hospitalization among patients without a history of cardiac conditions (IRR 1.54,  $P < 0.001$ ), as well as for those with specific pre-existing heart conditions:

- Acute MI: IRR 1.55 ( $P = 0.002$ )
- Afib: IRR 1.34 ( $P = 0.001$ )
- Chronic heart failure: IRR 1.48 ( $P < 0.001$ )
- Stroke: IRR 1.52 ( $P < 0.001$ )
- Ischemic heart disease: IRR 1.50 ( $P < 0.001$ )

“We show there’s significant increase in post-treatment hospitalization after abiraterone,” Lu-Yao said. “The same pattern was not observed for enzalutamide.”

Among men treated earlier in their disease course (before chemotherapy), and those with three or more cardiac conditions, men taking ENZ had a lower risk of hospitalization than those taking AA (IRR 0.59, 95% CI 0.44-0.79). In the post-chemotherapy setting, researchers found that men with hypertension had a higher rate of hospitalization (IRR 1.38, 95% CI 1.15-1.78).

Preliminary findings from the study that only examined the AA group were presented at the 2019 American Association for Cancer Research meeting in Atlanta.

Strengths of this study in-

cluded the use of a large population-based database with good representation of a range of ethnic/racial groups, as well as its longitudinal design, which presented data at the individual level. Limitations included no information available on treatment efficacy, and possible misclassification of CVD specifics, since information was obtained from Medicare files where misclassification and consequent underestimation of effects of extant CVD conditions are possible.

*MedPage Today*  
17 August 2019

## Sipuleucel-T

*(Continued from page 1)*

(76.8%) died of prostate cancer progression. The median time from the first infusion to prostate cancer death was 42.7 months (95% CI, 39.4-46.2 months). The incidence of sipuleucel-T-related SAEs was 3.9%. The incidence of CVEs was 2.8%, and the rate per 100 person-years was 1.2 (95% CI, 0.9-1.6). The CVE incidence among 11,972 men with mCRPC from the Surveillance, Epidemiology, and End Results-Medicare database was 2.8%; the rate per 100 person-years was 1.5 (95% CI, 1.4-1.7). One or more ACIs (abiraterone, enzalutamide, docetaxel, cabazitaxel, or radium 223) were received by 77.1% of the men after sipuleucel-T; 32.5% and 17.4% of the men experienced one- and two-year treatment-free intervals, respectively.

PROCEED provides contemporary survival data for sipuleucel-T-treated men in a real-world setting of new life-prolonging agents, which will be useful in discussing treatment options with men and in powering future trials with sipuleucel-T. The safety and tolerability of sipuleucel-T in PROCEED were consistent with previous findings.

## 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, "Second Generation..."

Enzalutamide and abiraterone acetate have benefitted men with advanced disease. Like all drugs, however, side effects do occur. In the package inserts, the following information is included:

**For Abiraterone:** "Use ZYTIGA with caution in patients with a history of cardiovascular disease. The safety of ZYTIGA in patients with LVEF < 50% or NYHA Class III or IV heart failure is not established."

**For Enzalutamide:** "Discontinue XTANDI for Grade 3-4 ischemic heart disease." Now a new report by Lu-Yao, et al. looks at the incidence of cardiac events in men being treated with these drugs from the SEER database. They found that having three or more cardiac conditions resulted in a greater risk for mortality.

It appears that using these drugs in men with heart disease poses a significant risk for adverse cardiovascular outcome. This raises a question whether a stronger warning message is needed.

**The Bottom Line:** Men with significant cardiac disease appear to be at significant risk for a cardiac event when receiving abiraterone or enzalutamide.

**P1, "First Results for..."** Does focal therapy have a future in men with low- or intermediate-risk prostate cancer? That question is being addressed in uncontrolled studies using HIFU, cryotherapy and now a new laser treatment following injection of nanospheres into lesions seen on mp-MRI. In this limited pilot study involving 12 men, two had residual dis-

ease in the treated lesions at three and 12 months. It is unclear if men had low- or intermediate-risk disease. Treatment was well tolerated and more men are being tested with this therapy.

Unfortunately, unless a proper study design is used, it may gain FDA approval without knowing if it prolongs survival, which is good for business but not necessarily good for patients. Sadly, the FDA uses different approval requirements for devices compared to drugs which, of course, makes little sense. The key question is whether cancer that is likely present elsewhere in the gland needs to be treated. Clearly, much more data are needed.

**The Bottom Line:** A new laser treatment using nanosphere injection has been developed with encouraging short-term results, but without a randomized trial its true benefit cannot be assessed.

### P1, "Largest Real-World..."

Although Provenge is an approved treatment for progressive metastatic prostate cancer that can increase survival, many people are skeptical about its benefit, in part because it is so expensive, and it has no effect on PSA or other measures of metastatic disease. A new case registry report draws attention to its potential survival impact. Higano, et al. reported a low incidence of side effects similar to the previous randomized trials. They also found one and two year treatment-free intervals of 33% and 17% respectively and a median survival of 31 months. In the original randomized trials, median survival improved 4.1 months over placebo and, at 36 months, sur-

vival increased from 23% to 31%. So the case registry supports relatively similar results. The problem is whether the net improvement has enough value.

**The Bottom Line:** A registry study shows relatively similar survival results compared to the randomized studies and men with progressive metastatic disease should discuss this option with their doctor.

**P2, "ARCHES..."** In the 1990's, Combined Androgen Blockade (CAB, castration plus an antiandrogen) showed improved survival in three of more than 30 randomized trials. However, many doctors doubted its benefit, so it was not widely prescribed. With the latest second-generation antiandrogens, it seemed appropriate to test their benefit combined with castration.

The result of the ARCHES study has now been reported in which enzalutamide was combined with castration in metastatic hormone sensitive disease and compared to castration plus placebo. Armstrong, et al. report that this combination significantly prolonged median time to radiographic disease progression compared to androgen deprivation therapy (ADT) plus placebo with little difference in significant side effects. They did not report the effect on overall survival and it remains to be seen whether the FDA will grant approval.

**The Bottom Line:** Combined androgen blockade using enzalutamide and castration appears to offer a benefit to men with metastatic castration sensitive disease.

**P2 "Salvage RP..."** Salvage

radical prostatectomy (RP) is not a widely popular treatment for recurrent prostate cancer, in part, because its impact on survival has not been well-studied and the incidence of complications is significantly higher compared to treatment-naïve men undergoing RP. A new report by Gontero, et al. compares the outcomes in men undergoing open vs. robotic salvage RP in an uncontrolled cohort accumulated between 2000 and 2014. The authors found a lower incidence of strictures and a lower incidence of severe urinary incontinence in the men treated using robotic surgery compared to the group having open surgery. Men were treated at 18 medical centers but it is unclear how many doctors at each center contributed patients.

There are a number of difficulties with evaluating these data. First, it is unclear how

(Continued on page 8)

### Join Us for: Prostate Cancer Pathways Free Educational Event and Webcast

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Theater from  
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**Register for the webcast at:**  
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**The Bottom Line** (Continued from page 7)

many different doctors were involved, making the actual number performed by each of them unclear. If only one doctor performed the operation at each center, it would mean that the average number of open RPs would be 10 per doctor or an average of less than one per year. This would hardly qualify as a good way to assess the complication rate to get meaningful information. The reader would benefit from know-

ing the actual number performed by each center. Also, the authors did not report whether some of the doctors had better or worse results than the entire group, so, it is quite possible that robotic RP is not different from open RP in very experienced hands. Second, the data were accumulated over 14 years and it would be helpful to know the distribution of cases using each method from year to year. Third, the authors do

report on the severe incontinence rates (three or more pads) but it would have been helpful to know the incidence of less severe incontinence in both groups.

**The Bottom Line:** Salvage RP has a high incidence of severe incontinence, even when it is done robotically, and there are no new data showing its impact on survival. Whether robotic RP truly has better results than open RP remains unclear.

**IMRT Vs. SRT**

(Continued from page 5)

**Interpretation:** Previous evidence (from the HYPO-RT-PC trial) suggested higher patient-reported toxicity with ultrahypofractionation. By contrast, our results suggest that substantially shortening treatment courses with stereotactic body RT does not increase either gastrointestinal or genitourinary acute toxicity.

**New Prostate Cancer Blood Test Could Reduce Biopsies** (Continued from page 6)

The current method of diagnosing prostate cancer by combining the PSA test with a biopsy leads to many pointless biopsies, over-diagnoses, and unnecessary treatments. This method can cause harm to individuals and waste precious time and resources in the healthcare system. "There is clearly a need for better selection of patients to undergo the biopsy proce-

dures," Prof. Lu urges. For the study, Lu and colleagues measured the new blood test in 98 males who had not yet had a biopsy and 155 others who had just received a diagnosis of prostate cancer but were not yet treated. All the participants were attending St. Bartholomew's Hospital in London. The researchers saw that the presence of CTCs in the

prebiopsy blood samples was predictive of aggressive prostate cancer that subsequent biopsies detected. In addition, from the level of CTCs, the team was able to assess the aggressiveness of the cancer. When combined with the PSA test, the CTC test was able to predict with 90% accuracy, which men would receive an aggressive prostate cancer diagnosis from

biopsy results. Further studies – using results from several independent centers – should now confirm these findings, note the researchers. The team expects the test to be available, following regulatory approval, around three to five years after researchers have completed validation studies.

*Medical News Today  
17 September 2019*

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## Between the Sheets...

October 2019

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

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

### QUESTION FROM PROSTATE CANCER SURVIVOR:

*I'm 71 years old and finished radiation therapy about six months ago. All went well and I am told that I have no evidence of disease. I do need to have nine months of hormone injections and, while I don't really want to do this, I feel that I have to do what the doctors have recommended.*

*My wife died ten years ago from breast cancer and, after a long period of grief (she was the best wife any man could have), I started dating someone my age shortly before being diagnosed. My 'friend' and I had a brief period of intense sexual connection and then came the diagnosis and treatment. We held off on sex while I was having the radiation, but now I would like to get things going again. The problem is that I have very little feeling in my genitals. It makes no difference if it's me alone or with my friend. Things down there just have no feeling at all. Is this normal?*

### RESPONSE FROM DR. ANNE KATZ:

*Androgen deprivation therapy (what is often called hormone therapy) is most likely the culprit here. It is well known that the lack of testosterone, as a result of the injections often prescribed along with radiation therapy, causes decreased genital sensitivity as you have described. Things may go back to normal when the nine months of treatment is over – but remember that the return to normal can take months.*

*So what can you do to help the situation? First, don't give up! It's wonderful that you have found a new relationship after an extended period of grief. It's also great that despite the lack of testosterone you have retained sexual interest (roughly 10 – 15% of men do). What may help is to use a vibrator. Yes, the subject of jokes on TV and among teenage boys (and maybe girls too) provides INTENSE and DIRECT stimulation to the genitals of both men and women (your friend may enjoy this as well so you are getting a 'twofer'!). This is a time and energy saver for many couples, as it provides stimulation and sensation in a way that the human hand cannot. For men, the vibrator can be used anywhere on the penis or testicles. There are many reliable brands available online – [www.LELO.com](http://www.LELO.com) have some beautiful examples that are as nice to look at as they are convenient to use (charge with a USB port and quiet as a whisper).*

Watch Dr. Katz' presentation on sexual health and intimacy from the Prostate Cancer Pathways for Patients and Caregivers event recorded at Englewood Health in Englewood, NJ on September 29, 2018.  
<https://www.youtube.com/watch?v=A2ZdDHw2WGY&t=8542s>.

Read previous issues of *Between the Sheets* at [www.ustoo.org/BTS](http://www.ustoo.org/BTS).

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

**Please email your question to: [ustooBTS@ustoo.org](mailto:ustooBTS@ustoo.org)**

**Or mail your letter to:**  
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Pssst!  
Check out our  
feature on sex and intimacy,  
*Between the Sheets*...

Advancements in prostate cancer research provide hope for finding a cure and lead to the discovery of new treatments to minimize the impact of a man's prostate cancer and maximize his quality of life. This regular *Hot SHEET* supplement includes some of the latest research from the Prostate Cancer Foundation ([www.pcf.org](http://www.pcf.org)).

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

### Artificial Intelligence and Prostate Cancer Diagnosis

The field of artificial intelligence (AI) started in the 1950s in the defense industry, and has evolved over the years. In the 2010s, new computer-based "deep-learning" methods were introduced that significantly accelerated the field. Physician-scientists are using this technology in the medical field to improve diagnostic methods. One such researcher is PCF-funded investigator Dr. Beatrice Knudsen, a Professor of Biomedical Sciences and Pathology and Director of Translational Pathology at Cedars-Sinai Medical Center in Los Angeles. She is one of the world's leading research pathologists, and is an expert on the diagnosis of prostate cancer and other diseases from tissue specimens.

In 2014, Dr. Knudsen and team began to apply **advanced AI** tools (machine learning and deep learning) in their studies. The team is aiming to answer key questions, including:

- Can a computer learn to **identify prostate cancer** in pathology slides?
- Can a computer **predict the risk** of existing or future prostate cancer **metastasis**?

When you think of diagnosing cancer, you might think of pink-and-purple slides with regular patterns (in benign tissue) vs. the "angry-looking" irregular patterns of cancerous cells. **Digital pathology is used today as a tool in diagnosis:** The FDA has approved a digital pathology slide scanner and monitor for digital reporting. This means the pathologist no longer needs to peek through a microscope, but can review slides on a computer screen and develop reports based on images displayed on computer monitors.

The same slides that are used to diagnose prostate cancer can also be used to train computer algorithms. Dr. Knudsen and team are using images from prostate needle biopsy slides as a starting point to develop machine learning and AI algorithms for digital diagnosis of prostate cancer. This computer-assisted diagnosis technology will **enable computers to pre-screen slides** for those that have the highest probability of harboring cancer. **Pathologists will be able to examine and confirm** the images that are selected by the computer because they have a high cancer probability. A study published by Memorial Sloan Kettering Cancer Center showed that computer-assisted diagnosis can help pathologists to focus their time on the most critical tissue pieces in the biopsy.

Machine learning is being developed to:

- Increase the efficiency of pathologists
- Shorten the amount of time to develop pathology reports for patients
- Improve the diagnostic accuracy of the algorithms
- Equalize the quality of pathology reports in medical practices throughout the community
- Improve the prediction of cancer severity
- Guide treatment decisions

Much progress has been made recently in digital computational pathology. **The speed of processing a single slide has significantly improved from ~8 hours in 2015 to under 1 minute in 2018.** Recent studies have described a computer-based tool that is able to diagnose prostate cancer with **~99% accuracy**. A PCF-funded Challenge Award team led by Dr. Knudsen and Dr. Isla Garraway of UCLA and the Greater West Los Angeles VA are investigating whether computer algorithms can be trained to recognize prostate cancers that will become lethal based on specific features present in the primary tumor. Results suggest that scores derived from biopsy slides can predict tumor stage at diagnosis.

With all of this technology, what is the role of the pathologist in the future? Despite the recent advances in digital pathology and AI, **Dr. Knudsen does not believe that AI will replace humans for routine diagnosis of human disease.**

**For more information visit [www.pcf.org](http://www.pcf.org), email [info@pcf.org](mailto:info@pcf.org), or call 1-800-757-2873.**