

INSIDE THIS ISSUE

Defining a Role for Immunotherapy in mCRPC	1
Veteran's Health Bill Promotes Comprehensive PCa Care Program	1
Prostatectomy of Mixed Mortality Benefit in Men with Prostate Cancer	1
Long-Term Unmet Supportive Care Needs of Prostate Cancer Survivors	2
AS vs. Immediate Treatment – Financial Incentives for Urologists	2
Doc Moyad's No Bogus Science: "Are Low-Carb Diets Groovy Now!?"	3
Combined Biopsy Strategy Improved Prostate Cancer Diagnosis	3
¹⁷⁷ Lu-PSMA Radionuclide Treatment in Men with Metastatic CRPC	4
PSMA PET/CT Better Detects Prostate Cancer Spread	5
Genomic Prostate Score Does Not Improve Risk Assessment	6
Its a Bust Adding Immunotherapy No Benefit in mCRPC	7



Hot SHEET

Us TOO INTERNATIONAL Prostate Cancer Education and Support Network

Defining a Role for Immunotherapy in mCRPC

Ipilimumab Active in Sub-Group with Favorable Pre-treatment Tumor Characteristics, Robust T-Cell Response

A small clinical study of checkpoint inhibitors for metastatic castration-resistant prostate cancer (mCRPC) identified favorable and unfavorable subgroups that might help inform use of the drugs in a disease that generally has proven unresponsive to immunotherapy.

Six of nine patients whose

tumors had favorable characteristics – defined by pre-treatment levels of two immune-cell parameters and/or robust antigen-specific T-cell responses – remained alive 33 to 54 months after treatment with ipilimumab (Yervoy). All nine of the patients had either radiographic or clinical progression-free survival (rcPFS) exceeding six months and overall survival (OS) greater than 12 months. Two of the patients had low tumor mutational burden (TMB), which is often associated with lack of response to immune therapy.

In contrast, all 10 patients with unfavorable tumor characteristics died within 10.3 months of treatment and

had rcPFS less than six months, as reported in *Science Translational Medicine*. “Our results indicate that immune checkpoint blockade can instigate T-cell responses to tumor neoantigens despite a low tumor mutational burden in prostate cancer (PCa),” lead study author Sumit Subudhi, M.D., PhD, of the University of Texas MD Anderson Cancer Center in Houston, said in a statement. “We found specific markers among a subset of men with the greatest benefit, such as T-cell density and interferon-γ signaling, that may help improve our ability to select patients for treatment with

(Continued on page 4)

Prostatectomy of Mixed Mortality Benefit in Men with Prostate Cancer

Over decades, death from any cause is lower in some men who undergo radical prostatectomy (RP), but observation alone may be a better choice in others with prostate cancer, according to a long-term follow-up of a randomized trial published in the journal *Urology*.

As Dr. Timothy J. Wilt told Reuters Health by email, “While surgery may have important mortality benefits in men with long life expectancies having clinically detected, intermediate-risk, and possibly high-risk prostate cancer, our results, together with other treatment trials, provide convincing evidence that observation

and PSA-based monitoring result in similar long-term mortality with less harm compared with surgery or radiation therapy (RT) for men with PSA-detected low-risk prostate cancer and many with intermediate- or high-risk disease.”

The trial included 731 men with localized prostate cancer who were 75 years or younger when they were randomized to RP or observation. Their PSA level was below 50 ng/mL and their life expectancy was at least 10 years.

Over the course of 21.1 years, 246 of the 346 men

(Continued on page 5)

Veteran's Health Bill Promotes Comprehensive Prostate Cancer Care Program

AUA Applauds Lawmakers for Support of Veterans with Prostate Cancer

The American Urological Association (AUA) today announced its support for the Veterans Prostate Cancer Treatment and Research Act, introduced on March 5 by Congressman Neal Dunn, MD (R-FL-3) and congressman Joe Cunningham (D-SC-1). This important bill supports the development and implementation of a Veterans Health Administration (VHA) healthcare program focused on a coordinated, comprehensive care for veterans with prostate cancer (PCa).

PCa is the most common non-skin cancer in American men, and the most commonly diagnosed cancer among U.S. veterans. The American Cancer Society estimates that 1 in 9 men will be diagnosed during their lifetime; in 2019 alone, nearly 175,000 men were diagnosed and more than 31,000 died from the disease. Furthermore, the National Institutes of Health reports that PCa is the most common cancer diagnosed in the Veterans Health Administration (VHA).

Despite these disturbing national statistics, there is no national clinical pathway for PCa care. The VHA has unparalleled systems and data resources and is uniquely capable of creating a true learning healthcare system to tackle its most common cancer diagnosis – leading to models that have the potential to affect all men.

The Veterans Prostate Cancer Treatment and Research Act specifically requires the VHA to:

(Continued on page 8)

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Long-Term Unmet Supportive Care Needs of Prostate Cancer Survivors: 15-Year Follow-Up from the NSW Prostate Cancer Care and Outcomes Study

Marariego CG, Juraskova I, Campbell R, Smith DP

Support Care Cancer, 16 March 2020 [Epub ahead of print]

To determine the prevalence, severity, and baseline associations of self-reported long-term unmet supportive care needs in a population-wide cohort of men with prostate cancer (PC), 15 years post-diagnosis, participants were drawn from the New South Wales (NSW) Prostate Cancer Care and Outcomes Study. Eligible men were diagnosed with PC between 2000 and 2002, aged less than 70 years at diagnosis, and completed a 15-year follow-up survey. Demographic and clinical data were collected at baseline. The validated Cancer

Survivors' Unmet Needs (CaSUN) Survey was administered to assess unmet needs. Of 578 eligible men, 351 completed CaSUN. Mean age was 75.8 (range 59-84) with a mean follow-up time of 15.2 years post-diagnosis. Over a third of men (37.4%) reported at least one unmet need at 15 years. Most frequently reported unmet needs pertained to the comprehensive cancer care (34.1%) domain. 87.2% of participants who reported problems with sexual function reported this need as moderate/severe. Higher diagnostic PSA levels (20+

ng/mL) at diagnosis were associated with future unmet needs (PSA 20+: OR = 4.80, 95% CI [1.33-17.35]).

Many PC survivors continue to report unmet needs 15 years post-diagnosis. There is a pressing need for clinicians to work together to coordinate PC care, and to proactively, regularly, and openly enquire about men's sexual adjustment to PC. The needs of PC survivors could better be met with more coordinated approaches to multidisciplinary care and timely interventions and support for chronic sexual dysfunction.

Active Surveillance vs. Immediate Treatment – Different Financial Incentives for Urologists

Zhang Z, Modi PK, Shahinian V, et al.

Urol Practice 7: 182-187, 2020

Introduction: We compared cumulative reimbursement to urologists following implementation of surveillance vs. immediate treatment. Active surveillance (AS) for prostate cancer is widely considered beneficial and cost-effective for low-risk patients, although many still receive immediate therapy. It is unknown whether reduced reimbursement may be a barrier to urologists recommending surveillance.

Methods: We used Medicare claims and a validated natural history model for low-risk prostate cancer to simulate annual reimbursements associated with active surveillance and immediate treatments, including surgery and radiation therapy. The model accounts for misclassification by biopsy under sampling, grade progression and discontinuation of surveillance due to patient preferences.

Results: Active surveillance provided approximately \$907 to \$2,041 less in the net present value of expected cumulative reimbursements for urologists over 10 years (\$1,711.80 to \$2,740.40 less over five years) compared to initial treatment. Sensitivity analysis showed that use of magnetic resonance imaging/ultrasound fusion based biopsies and frequency of biopsies and clinic visits under surveillance are major sources of uncertainty regarding reimbursement.

Conclusions: Urologists have little financial incentive to implement active surveillance. New payment models may be needed to bring financial incentives in line with the recommended treatment for patients with low-risk prostate cancer.

Get the Latest on COVID-19 and Prostate Cancer

Including resources, tips on holding virtual meetings, and an ongoing series of informational articles with some important comments regarding the coronavirus, cancer patients, and safety from Dr. Mark A. Moyad at www.ustoo.org/covid

To help us to help others by providing educational resources and support services at no charge, please consider donating at www.ustoo.org/donate

*Thank you!
And stay safe.*

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

“Low-Carb Diets (LCD) Should be Groovy Now?!”

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.

What tends to get missed in many recently completed prostate cancer (PCa) studies is that the average baseline body mass index (BMI) of subjects is getting closer to, or actually is 30. In other words, the average subject is overweight or obese, which is simply just a reflection of the weight issues going on in the general population. And, to add insult to injury, weight gain is a common side effect of androgen deprivation treatment (ADT). It would seem that one goal of PCa diet studies should be, at the very least, to help with weight loss because that is healthy overall, even if it is not proven to fight PCa. I believe serious kudos should be given to any diet study that preliminarily assists in helping many PCa patients lose weight safely and effectively.

Ergo, this recent multi-site

randomized six-month trial of a total of 57 men following a low-carbohydrate diet (LCD) vs. control in patients with biochemical recurrence (rising PSA after treatment) was interesting and should be given kudos. Why? There appeared to be no quick change overall in PSA doubling time (PSADT), but several heart-healthy lab tests improved, and the median weight loss was approximately 25 pounds with 4-5 inches of waist loss. Wow! Constipation and fatigue were more common at three months with LCD, which was not an issue at six months. Still, adequate fiber supplementation to reduce constipation and resistance/aerobic exercise to potentially reduce fatigue when going on an LCD should be discussed with your doctor if you are considering a diet plan such as this one. Keep in

mind that it is also possible that this diet could actually have an anti-PCa effect after further exploratory analysis (as suggested by these researchers after examining more data) or when following these participants for a longer time. Still, the profound weight loss, heart-healthy laboratory improvements, and, simply the fact that many men could reduce their carbohydrate and total overall caloric intake, is exciting! The researchers from this clinical trial should be given enormous kudos because diet studies are really hard to do for many reasons, including simply finding adequate funding for them.

I wish we would judge more diet plans on, not just PSA but whether they improve your overall health and simply make you heart healthier, which would improve the odds of living longer and

better. There are many ways to lose weight, but finding one that is generally safe, effective, and heart healthy in cancer patients should be given enormous kudos, respect, and attention. I am grateful to all the researchers that were a part of this study. Thank you!

Reference:

1. Freedland SJ, Allen J, Jarman A, et al. A Randomized Controlled Trial of a 6-month low carbohydrate intervention on disease progression in men with recurrent prostate cancer: Carbohydrate and Prostate Study 2 (CAPS2). *Clin Cancer Res* 27 February 2020 [Epub online]

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Combined Biopsy Strategy Improved Prostate Cancer Diagnosis

Combo Biopsy Missed Only 3.5% of the Most Aggressive Cancers

Low-grade prostate cancer (PCa) is associated with a very low risk of PCa-specific death and often does not require treatment; spread with high-grade PCa is much more likely and is responsible for most PCa deaths.

“PCa in Gleason grade groups (GG) 3-5 account for a majority of PCa deaths in the U.S. each year. The variation in disease lethality underscores the importance of accurate diagnosis,” noted Peter A. Pinto, MD, head of the Prostate Cancer Section of the National Cancer Institute Urologic Oncology Branch, and colleagues.

They found that combined use of magnetic resonance

imaging (MRI)-targeted biopsy and 12-core systematic biopsy led to enhanced detection of PCa vs. either method alone among men with MRI-visible lesions. Findings were published online in the *New England Journal of Medicine*.

“PCa is one of the only solid tumors diagnosed by performing systematic biopsies ‘blind’ to the cancer’s location. For decades this has led to overdiagnosis and subsequent unnecessary treatment of non-lethal cancers, as well as to missing aggressive high-grade cancers and their opportunity for cure,” said Pinto in a press release. “With the addition of MRI-

targeted biopsy to systematic biopsy, we can now identify the most lethal cancers within the prostate earlier, providing men the potential for better treatment before the cancer has spread.”

The most common method for the initial diagnosis and grading of PCa is transrectal, ultrasound-guided, 12-core systematic biopsy. Unlike biopsies for most other types of cancer targeting abnormalities found by imaging, systematic prostate biopsy provides a non-targeted, systematically spaced sampling of the prostate gland. This approach leads to potential inaccuracies with disease grading.

MRI-targeted biopsies merge images of suspected cancer taken earlier with real-time ultrasound technology. Studies have shown that MRI-targeted biopsies result in a higher rate of detection of high-grade cancers vs. systematic biopsy.

However, debate persists about whether MRI-targeted biopsy should be used in place of systematic biopsy or in conjunction with it. In the Trio Study, a substudy of the larger clinical trial, Pinto’s group evaluated the use of MRI-targeted biopsy, 12-core systematic biopsy, or the combination of the two in an

(Continued on page 6)

Defining a Role for Immunotherapy in mCRPC *(Continued from page 1)*

checkpoint blockade.

“Immune checkpoint inhibitors, such as CTLA-4 inhibitor ipilimumab and PD-1/L1 inhibitors, have the ability to induce durable T cell-mediated responses in a variety of tumors. However, the clinical benefits remain limited to a subset of patients with cancer,” Subudhi noted in the introduction.

Compared with melanoma and NSCLC associated with high TMB and tumor neoantigen frequency, prostate cancers have a low TMB and frequency of mutant neoantigens. Two phase III trials of ipilimumab showed no survival benefit for men with mCRPC, although a subgroup of men had durable clinical responses. Investigators continued to explore immune checkpoint blockade in mCRPC in a phase II trial to determine whether ipilimumab could elicit antigen-

specific T-cell responses in cancers that have a low TMB. The study involved a total of 30 men who had radiographic evidence of metastatic disease and tumor progression while on hormone therapy despite castrate serum testosterone levels. All but one of the men received at least one dose of ipilimumab, and 27 were evaluable for safety, efficacy, and translational analyses. Men had a median follow-up of 45.5 months from administration of ipilimumab.

The group had a median PSA-PFS of 1.7 months, median radiographic PFS of 3.0 months, and median OS of 24.3 months. The best radiographic response was stable disease, and treatment led to a disease control rate of 37%.

A total of 18 men did not meet the outcome criteria used to define the favorable subgroup. All 18 had rcPFS

less than six months, and 10 of the 18 also survived less than 12 months. Those 10 constituted the unfavorable group included in the correlational analyses.

“The 27 men had a median TMB of 76 nonsynonymous somatic mutations, considerably less than the TMB of melanoma and NSCLC (about 200), but consistent with other studies of mCRPC,” the authors said. TMB did not differ between the primary tumor or metastases.

Of the 27 men, 17 had sufficient peripheral blood mononuclear cells to evaluate T-cell responses to tumor associated antigens and neoantigens, including eight of nine men in the favorable subgroup and four of 10 in the unfavorable subgroup. The analyses showed that the favorable cohort increased CD8 T-cell density and increased expression of the

interferon-gamma response gene prior to starting treatment. Additionally, treatment with ipilimumab led to increased antigen-specific T-cell responses.

“We published a study several years ago showing that when you give anti-CTLA-4, interferon-gamma is produced by the T cells then PD-1 and PD-L1 are upregulated,” said senior author Padmanee Sharma, MD, PhD, also of MD Anderson. “That suggests that coming in with a combination might be better, and we have a larger ongoing study that is evaluating anti-CTLA-4 and anti-PD-1. We’re also looking at predictive biomarkers.”

The study was supported by Bristol-Myers Squibb, Stand Up to Cancer, the Prostate Cancer Foundation, and the National Institutes of Health/National Cancer Institute.

MedPage Today
2 April 2020

Early Prostate-Specific Antigen Changes and Clinical Outcome Following ¹⁷⁷Lu-PSMA Radionuclide Treatment in Patients with Metastatic Castration-Resistant Prostate Cancer

Gafita A, Heck M, Rauscher I, et al.

J Nucl Med 28 February 2020; Epub

Background: PSA is widely used to monitor treatment response in men with metastatic castration-resistant prostate cancer (mCRPC). However, PSA measurements are considered only after 12 weeks of treatment. We aimed to evaluate the prognostic value of early PSA changes following ¹⁷⁷Lu-labelled prostate specific membrane antigen (LuPSMA) radionuclide treatment in mCRPC patients.

Methods: Men who were treated under a compassionate access program with LuPSMA at our institution and had available PSA values at baseline, at six weeks after treatment initiation were included in this retrospective analysis. Patients were as-

signed to three groups based on PSA changes: 1) response: $\geq 30\%$ decline, 2) progression: $\geq 25\%$ increase and 3) stable: $< 30\%$ decline and $< 25\%$ increase. The co-primary end points were overall survival (OS) and imaging-based progression-free survival (PFS). The secondary end points were PSA changes at 12 weeks and PSA flare-up.

Results: We identified 124 eligible patients with PSA values at six weeks. A $\geq 30\%$ decline in PSA at 6 weeks was associated with longer OS (median 16.7 months; 95% Confidence Interval [CI], 14.4-19.0) vs. men with stable PSA (median: 11.8 months; 95%CI 8.6-15.1; $P = 0.007$) and progression (median: 6.5 months; 95%CI

5.2-7.8; $p < 0.001$). Men with $\geq 30\%$ decline in PSA at six weeks also had a reduced risk of imaging-based progression vs. men with stable PSA (Hazard Ratio [HR]: 0.60; 95%CI 0.38-0.94; $P = 0.02$), while men with PSA progression had a higher risk of imaging-based progression vs. those showing stable PSA (HR: 3.18; 95%CI 1.95-5.21; $p < 0.001$). The percentage changes of PSA at six and 12 weeks were highly associated ($r = 0.90$; $p < 0.001$). 29 of 31 (94%) men who experienced early PSA progression at 6 weeks achieved biochemical progression at 12 weeks. Overall, only one of 36 (3%) men with PSA progression at six weeks achieved any PSA decline at 12 weeks (1% of

the entire cohort). Limitations of the study included its retrospective nature and the single center experience.

Conclusion: PSA changes at 6 weeks after LuPSMA initiation are an early indicator of long-term clinical outcome. Men progressing by PSA after 6 weeks of treatment could benefit from a very early treatment switch decision. PSA flare-up during LuPSMA treatment is very uncommon. Prospective studies are now warranted to validate our findings and potentially inform clinicians earlier on the effectiveness of LuPSMA.

Prostatectomy of Mixed Mortality Benefit in Men with Cancer *(Continued from page 1)*

assigned to surgery died, compared to 269 of 367 assigned to observation (68% vs. 73%, $P=0.044$, a statistically significant difference). The restricted mean survival time in the surgical group was 13.6 vs. 12.6 years in the observation group (95% confidence interval, 0.0 to 2.0 years).

Results did not significantly vary by patient or tumor characteristics, but differences favoring surgery were greater in men who were white, aged less than 65 years and who had better health status. Overall, say the researchers, “Absolute effects were much smaller in

men with low-risk disease, but were greater in men with intermediate-risk disease, although not in men with high-risk disease.”

“Early intervention results in morbidity and negatively impacts urinary, sexual, and erectile function, as well as physical comfort and activities of daily living,” Dr. Wilt pointed out.

He concluded, “Clinicians should discuss these findings with their patients, and target early interventions to individuals needing and benefiting while reducing harms of ineffective treatments and/or overtreatment.”

Dr. Jim C. Hu, a professor of urologic oncology at New York Presbyterian/Weill Cornell, in New York City, told Reuters Health by email, “The challenge of randomized trials for prostate cancer is the long period of time needed for meaningful differences to occur and, in turn, practice patterns change as we wait for these events.

“The authors note that the study was not powered for subgroup analysis and results should be interpreted with caution; however, this is the most meaningful way to look at this research,” he added. “For instance, it is reassuring that surgery had no benefit

for men with low-risk prostate cancer: at present most men with low-risk disease opt for active surveillance.”

Also, he said, “white men were more likely to benefit from surgery vs. blacks and others; surgery was more likely to be beneficial in younger men and those with no comorbid conditions.”

Dr. Hu concluded, “taken together, surgery has a benefit in younger, healthy men, confirming the findings of the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4).”

Reuters Health
11 March 2020

PSMA PET/CT Better Detects Prostate Cancer Spread

Improved Metastases Detection Altered Treatment Course for Twice as Many Men

In men with high-risk prostate cancer, imaging with prostate-specific membrane antigen (PSMA) PET-CT prior to curative surgery or radiotherapy (RT) proved far more accurate than conventional imaging for detecting metastatic disease, a randomized trial found.

“Among 295 evaluable men, ⁶⁸gallium PSMA-11 PET-CT imaging had an accuracy of 92% (area under the curve of the receiver operating characteristic curve) vs. 65% with standard CT imaging and bone scans ($P < 0.0001$, a statistically significant difference),” reported Michael Hofman, MBBS, of the Peter MacCallum Cancer Centre in Melbourne, Australia, and colleagues in *The Lancet*.

There were fewer equivocal cases of metastatic disease with PSMA PET/CT (7 vs. 23% with conventional imaging), and the novel imaging method altered the course of disease management for twice as many men following first-line imaging (28 vs. 15%, $P=0.008$, a statistically sig-

nificant difference). In those who underwent second-line imaging – for men with no more than two unequivocal metastases – change in treatment occurred in 27% of those that crossed over to PSMA PET/CT, but just 5% of those switching to conventional imaging.

“Taken together, our findings indicate that PSMA-PET/CT scans offer greater accuracy than conventional imaging and can better inform treatment decisions,” Hofman said in a statement. “We recommend that clinical guidelines should be updated to include PSMA PET/CT as part of the diagnostic pathway for men with high-risk prostate cancer.”

PSMA “is a cell-surface glycoprotein overexpressed on prostate cancer cells,” according to background information in the paper. Using radiolabeled small molecules that bind these cells, PSMA PET/CT can detect tumor presence throughout the body. Men receiving PSMA PET/CT were also exposed to

significantly lower radiation levels than with conventional imaging (8.4 vs. 19.2 millisieverts, respectively).

“Current medical imaging techniques often fail to detect when the cancer has spread, which means some men are not given the additional treatments they need,” co-author Declan Murphy, MBBCh, also of Peter MacCallum Cancer Centre, said in a statement. “Our findings suggest PSMA-PET/CT could help identify these men sooner, so they get the most appropriate care.”

In an accompanying editorial, Caroline Moore, MD, of University College London, pointed to one limitation in the study – the way metastasis was defined – that may have biased the results in favor of PSMA PET/CT.

Metastatic disease was defined as either a bone lesion changing to sclerotic or blastic on follow-up imaging, or histologic confirmation of a metastatic site – this “hard criteria” was met in just 23% of the 87 men in the study

with metastases. Alternatively, metastasis could also be established via three “soft criteria,” which included rising PSA levels at six months, increases or decreases in lesion number or size on subsequent imaging, a lesion associated with clinical symptoms, and others.

“Although these criteria reflect a real-world approach, where men having RT will not have histological confirmation of nodal disease, some men might have had microscopic disease that was not detected by either modality,” wrote Moore. “Also, some men might have had false-positive findings that were not assessed further.”

In the study, she noted that a small group of men still went on to radical treatment despite presence of metastatic disease on PSMA PET/CT.

“Introduction of new imaging modalities, such as PSMA PET-CT, with improved sensitivity in detecting small-volume metastases, brings

(Continued on page 8)

Genomic Prostate Score Does Not Improve Risk Assessment

A genomic prostate score (GPS) has little value in predicting adverse outcomes in men who have undergone a period of active surveillance (AS) before having a radical prostatectomy (RP), according to a study published online in the *Journal of Clinical Oncology*.

The hazard ratio (HR) for adverse pathology using the 17-gene Oncotype DX Genomic Prostate Score did not reach statistical significance in a multivariate model (HR, 1.17; P=0.066). This model took into account risk factors such as the PSA density (PSAD) and the Gleason grade group at diagnosis.

“In our study, the independent association of GPS with adverse pathology after initial AS was not statistically significant,” reported Daniel W. Lin, MD and colleagues of the Fred Hutchinson Cancer Research Center in Seattle. There was also no associa-

tion between the GPS and having upgraded biopsy findings during AS.

AS is the “preferred management strategy” for men with low-risk prostate cancer, observed Dr. Lin and colleagues, but its use is often tempered by the worry that undetected pathology may be present that is not found by routine clinical measures such as PSA. In their study, the investigators looked to see if using the GPS could help risk-stratify men with low-risk prostate cancer planning to undergo AS.

They noted that the biopsy-based genomic test had been shown to predict adverse surgical pathology and recurrence in men with low- and intermediate-risk prostate cancer who had undergone immediate RP. The team therefore wanted to clarify the test’s role in men who had been initially managed with a period of AS.

Investigators calculated GPS by retrospectively analyzing diagnostic biopsies prospectively collected from 432 men in the Canary Prostate Active Surveillance Study. The primary endpoint was adverse pathology in men who underwent RP after initial AS. Adverse pathology in the study was defined as a Gleason grade of 3 or greater, pathological staging of pT3a or higher (with or without lymph node metastases [N1]), or both.

After a median follow-up of 4.6 years, 167 (39%) men experienced upgrading of their prostate cancer at a surveillance biopsy, with 51 (12%) being upgraded to a Gleason grade group of 3 or higher. A total of 101 (23%) men had RP at a median of 2.1 years after their diagnostic biopsy, and just over half (52/101, 51%) had adverse pathology at this time point. GPS was associated with ad-

verse pathology when the diagnostic Gleason grade group was taken into account (HR, 1.18; P = 0.030, *a statistically significant result*) but not when the investigators adjusted for both PSAD and diagnostic Gleason grade group. By contrast, PSAD (HR 1.75; P = 0.025) was significantly associated with adverse pathology.

“Adding GPS to a model containing PSAD and diagnostic [Gleason grade group] did not significantly improve risk stratification for [adverse pathology] over the clinical variables alone,” Dr. Lin and colleagues concluded.

This work was supported by the Canary Foundation, the Department of Defense, the National Institutes of Health, and Genomic Health. The authors disclosed relationships with Genomic Health and other companies.

Medscape Medical News
25 March 2020

Combined Biopsy Strategy Improved Prostate Cancer Diagnosis *(Continued from page 3)*

attempt to define the most effective method for PCA diagnosis.

Men eligible for the substudy had an elevated PSA level or abnormal digital rectal exam and were eligible for prostate MRI. Men with detected PCA could enroll in the study if they consented to prostate biopsy. Of this group, 2,103 men had MRI-visible lesions and were included in the analysis. They underwent both systematic and MRI-targeted biopsies at the same center.

The primary outcome was cancer detection according to Gleason GG. Clinically insignificant disease was defined as GG 1. PCA with favorable intermediate risk or worse was defined as GG 2 or higher, and GG 3 or higher was defined as cancer with

unfavorable intermediate risk or worse. Upgrading and downgrading of GG from biopsy to whole-mount histopathological analysis of surgical specimens were recorded among the men who underwent subsequent radical prostatectomy (RP).

Pinto and team found that systematic biopsy alone and MRI-targeted biopsy alone diagnosed PCA in 1,104 and 1,084 men, respectively. However, adding MRI-targeted biopsy to systematic biopsy led to 208 (9.9%) more diagnoses, 59 (28.4%) of which were clinically significant (GG 3 or greater), vs. either method alone.

The combination strategy also led to upgrading to a higher GG in 458 (21.8%) men. Overall, PCA was diagnosed in 1,312 men (62.4%)

with the combination of the two biopsy methods, and 404 (19.2%) subsequently underwent RP.

Cancer detection rates with MRI-targeted biopsy were significantly lower than with systematic biopsy for GG 1 PCA and significantly higher for GGs 3-5 (P <0.01 for all comparisons). Thus MRI-targeted biopsy detected more clinically significant (GG ≥3) prostate cancers.

Among the men who underwent RP, Pinto and team found that systematic biopsy alone underdiagnosed about 40% of cancers, and MRI-targeted biopsy alone underdiagnosed about 30% of cancers, while combined biopsy underdiagnosed 14.4% of the cancers. In addition, while systematic biopsy and MRI-targeted biopsy underdiag-

nosed 16.8% and 8.7% of the most aggressive cancers, respectively, combined biopsy missed only 3.5% of the most aggressive cancers.

The researchers acknowledged that results were obtained at only one institution and might not be generalizable to institutions with less experienced practitioners. Use of one physician to perform the systematic biopsy and another to perform the MRI-targeted biopsy is not representative of actual practice patterns, they noted. There was also the possibility of selection bias in the RP cohort, since RP was not performed in all men with a PCA diagnosis.

MedPage Today
2 April 2020

Its a Bust Adding Immunotherapy - No Benefit in mCRPC

No clinical benefit was seen from adding the immune checkpoint inhibitor atezolizumab (Tecentriq, Genentech) to standard treatment with the androgen receptor inhibitor enzalutamide for men with metastatic castration-resistant prostate cancer (mCRPC).

“Median overall survival, the trial’s primary endpoint, was numerically, but not statistically, longer among patients with mCRPC who were randomly assigned to receive treatment with enzalutamide alone,” reported lead investigator Christopher J. Sweeney, MBBS, from the Dana-Farber Cancer Institute in Boston. The finding comes from the phase 3 IMbassador250 trial.

This was “the first phase 3 trial to investigate a checkpoint inhibitor therapy combination in metastatic CRPC. It revealed no evidence of a difference in cancer control between arms, whether it be measured by radiographic progression-free survival or time to PSA progression,” he said.

“Adding insult to injury, the investigators could not identify, on the basis of expression of programmed death ligand-1 (PD-L1), a subpopulation of men who might have benefited from the combination therapy, and adverse events were more frequent than with enzalutamide alone,” Sweeney said.

Sweeney presented the results online during the American Association for Cancer Research (AACR) 2020 virtual meeting.

What Happened?

“It sounded good on paper: the clinical rationale for

combining an immune checkpoint inhibitor with enzalutamide was that there was evidence that immunotherapy with sipuleucel-T had efficacy in CRPC, and initial investigations with ipilimumab that showed an increase in antigen-specific T cells following treatment with sipuleucel-T,” Sweeney said.

“In addition, there has been evidence that programmed death-1 (PD-1) blockade may have activity following the development of resistance to enzalutamide and that monotherapy with atezolizumab, an inhibitor of PD-1 and PD-L1, was associated with long-term disease control in mCRPC,” he added.

However, these new results “indicate that neither anti-PD-1/PD-L1 monotherapy or the anti-PD-1/PD-L1 combination therapy with enzalutamide are likely to provide improved clinical benefit over standard-of-care agents for men with mCRPC whose disease progressed on prior hormonal therapy and prior chemotherapy,” commented Padmanee Sharma, MD, PhD, from the University of Texas MD Anderson Cancer Center in Houston, who was the invited discussant.

Discussing why the IMbassador250 trial may have failed, she noted that prostate cancer has few T cells, and therefore targeting PD-1 or PD-L1 would not have much of an effect.

“There are multiple immunosuppressive pathways within the prostate tumor microenvironment, and the PD-1/PD-L1-targeting agents may not sufficiently target all these immunosuppressive pathways,” she said.

In addition, “there are few mutations in prostate cancer, and as a result, the effector T cells may not be able to recognize an adequate number of antigens to lead to an antitumor response,” Sharma said.

Study Details

The IMbassador250 study was a phase 3, multicenter, randomized, open-label study involving 759 men with metastatic, locally advanced, or incurable CRPC who had experienced disease progression with abiraterone, were ineligible or refused a taxane-based regimen, or for whom a taxane regimen had failed.

After stratification on the basis of prior taxane therapy, presence of liver metastases, lactate dehydrogenase levels, and pain severity in the past 24 hours, the patients were randomly assigned to receive either enzalutamide 160 mg daily or the same regimen plus atezolizumab 1200 mg intravenously every three weeks. Treatment continued until loss of clinical benefit or unacceptable toxicity.

Median overall survival (OS) was 15.2 months with the combination, compared with 16.6 months for enzalutamide alone, which translated into a hazard ratio for death with the combination of 1.12 ($P = 0.28$, *not a statistically significant difference, e.g., ns*).

The 12-month OS rates were 60.6% for enzalutamide alone vs. 64.7% for the combination.

An analysis of OS by the clinical subgroup found no advantage from the combination over enzalutamide alone for prior docetaxel exposure, prior local thera-

py, measurable disease status, the presence of visceral or nonvisceral metastases, or PD-L1 expression.

Radiographic progression-free survival was 4.2 months with atezolizumab/enzalutamide vs. 4.1 months with enzalutamide alone ($P = ns$). Time to PSA progression was 2.8 months in each arm.

Among patients with measurable disease at baseline, the overall response rates were 14% in the combination group and 7% in the group that received enzalutamide alone. Two patients in the combination group and one in the enzalutamide-only group had complete responses.

Grade 3 or 4 treatment-related adverse events (AEs) occurred in 28% of patients who received the combination, vs. 10% who received enzalutamide alone. Seven patients in the combination arm and one in the enzalutamide arm died from treatment-related causes. Treatment-related serious AEs were also more frequent with the combination (14 vs. 3%), and AEs that led to discontinuation of any treatment component occurred in 14% of men in the combination arm, vs. 6% in the enzalutamide-alone arm.

The study was sponsored by F. Hoffman-La Roche. Enzalutamide was provided by Astellas and Pfizer. Sweeney has advisory or consulting roles and/or has received research funding from the companies. Sharma has consulting roles, has engaged in advisory board activities, or owns stock in for various companies, not including the sponsors.

Presented at AACR 2020: Abstract CT014

Medscape Medical News
29 April 2020

VA Comprehensive Prostate Cancer Care Program

(Continued from page 1)

- Create a national PCa clinical pathway to cover the disease from screening to end of life, and update it as needed. The pathway would strive to reflect relevant PCa care guidelines.
- Develop a national PCa care implementation program. This would be administered by a nationally-recognized leader in PCa care who would coordinate efforts across relevant VA entities, measure PCa quality and costs and create a national PCa education plan aimed at administrators, providers and patients.
- Design a Prostate Cancer Registry and Research Program. The aim of the program is to evaluate all aspects of the disease continuum from screening to end-of-life care, define optimal ways to implement recommended

guidelines, coordinate care, discover new insights into disease treatment and evaluate comparative effectiveness of existing treatments for health services, basic science, as well as translational medicine and clinical trials.

“The VHA – as a national system for healthcare delivery – is perfectly positioned to create this program,” said AUA President John H. Lynch, MD. “We’d like to thank Dr. Dunn and Rep. Cunningham for introducing this very important bill to help understand how we can define and deliver optimal care for men with PCa.”

The AUA is proud to support this important piece of legislation, which we believe will standardize treatment options and result in improved outcomes for PCa patients.

PRNewswire
5 March 2020

PSMA PET/CT Detects Prostate Cancer Spread

(Continued from page 5)

both challenges and opportunities,” she continued. “In particular, when men test negative on conventional imaging, and PSMA PET-CT shows small-volume metastatic disease, what should we do?”

From 2017 to 2019, the proPSMA study randomized 302 men with high-risk prostate cancer 1:1 to either standard CT imaging plus a bone scan or to PSMA PET-CT across 10 Australian sites. Median subject age was 68. High-risk disease was defined as one of the following: clinical stage \geq cT3, a PSA level \geq 20 ng/mL in the 12 weeks prior to randomization, or International Society of Uro-pathology grade group 3-5. Of the 295 men with follow-up, 30% had either pelvic nodal metastases or distant metastases. Sensitivity was improved with PSMA PET/CT, at 85% compared to 38% with conventional imaging,

as was specificity (91 vs. 98%, respectively).

In subgroup analyses, PSMA PET/CT was more accurate at detecting both pelvic nodal metastases (91 vs. 59% with conventional imaging) and distant metastases (95 vs. 74%).

Hofman disclosed grants from the Prostate Cancer Foundation of Australia, Movember, the Peter Mac-Callum Foundation, the U.S. Department of Defense, and the Victorian Cancer Agency; and other relationships with Ipsen, Sanofi Genzyme, and Janssen. Coauthors reported grants from or financial relationships with the Prostate Cancer Foundation of Australia, Mundipharma, Janssen, Ferring, Telix Pharmaceuticals, Astellas, Janssen, Bayer, and Ipsen.

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Between the Sheets...

May 2020

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. Jeffrey Albaugh, Director of Sexual Health at NorthShore University HealthSystem and at Jesse Brown VA Medical Center in Chicago, IL. Dr. Albaugh is a funded researcher, a board certified advanced practice urology clinical nurse specialist, and a board certified sexuality counselor. In addition to his many publications in peer reviewed journals and chapters in books on sexual dysfunction, Dr. Albaugh published *Reclaiming Sex and Intimacy After Prostate Cancer Treatment*. He has been quoted in media and publications as an expert in the treatment of sexual dysfunction, and is a member of the Us TOO Board of Directors.

QUESTION FROM PROSTATE CANCER SURVIVOR:

I have been feeling it is difficult to connect with others due to the coronavirus (in addition to the difficulty in continuing to deal with prostate cancer). Do you have any guidance?

RESPONSE FROM DR. JEFFREY ALBAUGH:

How to have hope in challenging times? Hope is a powerful, transforming force and an intrinsic part of each of us. When diagnosed with cancer, fear (rather than hope) sometimes becomes the dominant force in your life. As you mobilize hope, life dramatically changes for the better. I have found through my patients that hope can change everything. As Maya Angelou said, "Hope and fear cannot occupy the same space at the same time. Invite one to stay." Hope can dispel fear. Our world is facing the COVID-19 pandemic and, although infectious diseases are nothing new in our world, a new novel infectious disease that is impacting people across the globe to various degrees, including fighting for their lives, has changed how we live, how we interact and most everything about our lives. It definitely impacts our connection to others as most of us are living under a stay at home order and isolating ourselves physically from others, including our loved ones. As we struggle with not being able to make face-to-face eye contact and physically show our affection to the many family and friends we love, we do our best to stay connected through phones, video and social media. Make no mistake, each of us is hard wired for human connectedness (Goleman, D. 2007; Maslow, A. 1966) and as we see our way through the COVID-19 pandemic and future infectious diseases, we must find meaningful ways to be connected with other human beings. Brene Brown defines connection as the energy that exists between people who feel seen, heard and valued by the other person without feeling judged (Brown, B., 2003). Who doesn't want to feel seen, heard and valued by others? Now more than ever we need deep rooted connection with other human beings. This connectedness with others can magnify hope. If you are lucky enough like me, to be isolated at home with your partner whom you love, continue to take time for intimacy (communication on all levels) and connectedness. If you have been separated from your partner, when you are able to be together, take time to reconnect and re-establish intimacy. I can't think of anything more important than a deep sense of connection with the partner you love, as well as your friends and family.

Goleman, D. (2007). *Social Intelligence*. New York: Bantam.

Maslow, A. H. (1987). *Motivation and personality (3rd ed.)*. Delhi, India: Pearson Education.

Brown, B. (2010). *The Gifts of Imperfection*. Center City, MN: Hazelden Publishing.

You can access the new edition of my book or download a free copy of my original book at www.drjeffalbaugh.com.

Watch Dr. Albaugh's presentation on sexual health and intimacy from the *Prostate Cancer Pathways for Patients and Caregivers* event recorded at NorthShore University HealthSystem in Skokie, IL on November 3, 2018 at <https://www.youtube.com/watch?v=Hiq0dDEb1l0&t=4483s>.

Read previous issues of *Between the Sheets* at 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

Or mail your letter to:

Us TOO International
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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).

Treatment of Oligometastasis: Results from the ORIOLE Study

PCF's medical writer Janet Worthington sat down (virtually) with Johns Hopkins radiation oncologist Phuoc Tran, M.D., Ph.D., to discuss his recent trial of radiation therapy.

To the growing list of strategies for attacking prostate cancer, let us add this approach: **Whack-a-Mole**.

That's how Dr. Tran describes it to his patients. The actual scientific name for this highly sophisticated strategy is stereotactic ablative radiotherapy (SABR, highly focused, intense doses of radiation), for men with *oligometastasis* – up to three small bits of cancer that have broken away from the main prostate tumor and started to grow elsewhere.

His strategy was a new one – part of a general rethinking of what represents curable prostate cancer. The boundary used to be very clear: prostate cancer was either confined to the prostate or prostate bed, or it wasn't. A man with only one metastasis was believed to face the same fate, eventually, as a man with widespread metastases. It was just a matter of time.

But Tran believed that the lines of prostate cancer were **not so clear-cut** as scientists had assumed; that instead of two circles – localized and metastatic cancer – that didn't connect, we might be dealing with a **Venn diagram, with oligometastasis as the critical area where the two circles overlap**. "It may be that the window of curability is wider than we thought," he said, and we all hoped that he was right.

Tran and colleagues at Johns Hopkins, Stanford, and Thomas Jefferson University recently published results of the ORIOLE Phase 2 clinical trial in *JAMA Oncology* (<https://jamanetwork.com/journals/jamaoncology/fullarticle/2763312>). The results are promising: 54 men with oligometastasis were randomly assigned either to treatment with SABR or to observation. To detect and keep track of the oligometastases, the study used PSMA-PET scanning, which uses a small molecule linked to PSMA (prostate-specific membrane antigen, found on the surface of prostate cancer cells) as a radioactive tracer. This PSMA-targeting tracer can highlight areas of cancer as small as a BB – much smaller than can be seen on regular PET or CT imaging. "PSMA-PET allows us to treat lesions we otherwise couldn't see," Tran explains. "A CT or bone scan would miss those lesions, and patients would presumably not do as well."

At six months, 61 percent of the men in the observation group progressed – compared to **only 19 percent of the men who received SABR**. "We also saw a **significantly decreased risk of new metastatic lesions** using PSMA PET-CT," says Tran. "The men in the SABR group did considerably better. This is a definite signal that we can perhaps modify metastatic disease."

This was a Phase 2 study, and "we need larger Phase 3 trials," he says. "**But this is very positive, and we hope that in the future, we will be able to change the course of metastatic disease in some men.**"

"**It's like Whack-a-Mole:**" Tran and colleagues have learned from this and other research that men with oligometastasis fall into three basic groups. "Some men do really well after one course of SABR," with no recurrence of cancer. A second group of men have a small recurrence. "Another site pops up; a *microscopic* metastasis that we couldn't see before establishes itself into a *macroscopic* metastasis. It's a limited return of cancer and it responds to another round of SABR." Then some men, after a few months, have multiple new areas of cancer. "For these men, the SABR doesn't control the disease at all."

"**Imagine a green lawn, with one or two dandelions,**" Tran tells his patients: "You can pluck those two or three weeds, and wait and see. Sometimes you get lucky; sometimes another weed or two pops up, and you pluck them. It's like Whack-a-Mole. You can do that for a while," with repeated SABR treatments.

"That probably won't work in every man," Tran says. "Unfortunately, sometimes there will be a whole bunch of seeds all at once, and at that point, you need weed killer all over the lawn," or systemic therapy. However, SABR plus ADT, androgen-blocking drugs, or chemo might one day provide "the multipronged attack required to cure this disease."

More and larger studies are needed but, in the future, Tran envisions men with oligometastasis will require more vigilant monitoring, and ideally, regular follow-up PSMA-PET scanning.

For more information visit www.pcf.org, email info@pcf.org, or call 1-800-757-2873.