Apalutamide Benefit Sustained in Metastatic CSPC Regardless of Next Therapy

Early use of the androgen receptor antagonist apalutamide for metastatic castration-sensitive prostate cancer (mCSPC) has a sustained carry-over benefit regardless of subsequent therapy, an exploratory analysis of the TITAN trial suggests.

Previous trial results for all 1,052 men randomized showed significant improvements in radiographic progression-free survival (PFS) and overall survival (OS) from adding apalutamide vs. placebo to androgen deprivation therapy, leading to recent Food and Drug Administration approval of the drug for mCRPC.

In the new analysis, investigators assessed PFS2, measured from time of randomization to investigator-determined disease progression or death, among the 277 men who went on to receive a subsequent life-prolonging therapy after progression on their initial trial.

Results reported at the 2020 Genitourinary Cancers Symposium (GuCS) showed that the risk of PFS2 events was similarly reduced for men who had initially received apalutamide vs. placebo, regardless of whether their next therapy was a new hormonal therapy (32% reduction in risk) or a taxane (37% reduction in risk).

“The PFS2 benefit is an indicator of effective early intensification of treatment, is consistent with the OS benefit we have seen with this agent, and together shows totality of the treatment trajectory,” reported Neeraj Agarwal, MD, the study’s lead investigator. “These results may assist with counseling of patients with metastatic castration-sensitive prostate cancer (mCSPC) who go on to receive a subsequent life-prolonging therapy after progression on their trial therapy.”

Hypofractionated Radiotherapy for Prostate Cancer Stands the Test of Time

In men with localized prostate cancer (PCa), a hypofractionated radiotherapy (RT) regimen that cuts treatment time in half continues having noninferior long-term efficacy relative to a conventional RT regimen, an update of the CHHIP trial shows.

The 3,216 men in the phase 3 trial had node-negative T1b-T3a PCa and were evenly assigned to a conventional regimen of 74 Gy delivered in 37 fractions, a hypofractionated regimen of 60 Gy in 20 fractions, or a hypofractionated regimen of 57 Gy in 19 fractions. All regimens were delivered with intensity-modulated RT techniques.

The trial’s five-year results, previously reported, showed noninferiority of the 60-Gy vs. the 74-Gy regimen on risk of biochemical or clinical failure (hazard ratio [HR], 0.84), prompting recommendation of the former as a new standard of care for localized PCa. Noninferiority could not be established for the 57-Gy regimen.

Eight-year results were essentially the same, confirming noninferiority of the 60-Gy (HR, 0.85) but not the 57-Gy regimen. Moreover, bowel and bladder toxicity remained low across regimens.
Phase II Trial of Enzalutamide and Androgen Deprivation Therapy with Salvage Radiation in Men with High-Risk Prostate-Specific Antigen Recurrent Prostate Cancer: The STREAM Trial


Eur Urol. 13 February 2020; Epub ahead of print

Salvage external beam radiotherapy (RT) with androgen deprivation therapy (ADT) improves survival over RT in men with prostate cancer (PCa) and a rising PSA after radical prostatectomy (RP).

Aim: To investigate the safety and efficacy of enzalutamide concurrent with salvage RT and ADT.

Patients and Methods: This was a three-center prospective phase 2 single-arm trial (NCT02057939) of men with Gleason 7-10 PCa and PSA recurrence ranging from 0.2 to 4.0 ng/dL within four years of RP, no prior hormonal therapy, and no radiographic evidence of metastases. We enrolled 38 men; 37 completed therapy and were evaluable with testosterone recovery at two years.

Treatment: Six months of ADT with 160 mg/day enzalutamide and 66 Gy RT to the prostate bed.

Endpoints: The primary end-point was improved two-year progression-free survival (PFS) over historical controls. Secondary objectives included three-year PFS, safety, and patient-reported quality of life (QOL).

Results: The primary end-point was 65% (95% confidence interval [CI]: 47, 78) vs. 51% (95% CI: 33, 67) in a trial of men with similar eligibility treated with salvage RT and adjuvant docetaxel. The three-year PFS was 53%. Eleven (29%) men experienced grade 3 (G3) toxicities, and there were no G4-5 or unexpected toxicities. QOL data suggest modest worsening of bowel, bladder, and hormonal symptoms at three months, with recovery by 24 months in most men.

Conclusion: Salvage RT with enzalutamide and ADT for men with PSA recurrent high-risk PCa post-RP is safe and demonstrates encouraging efficacy, warranting prospective controlled phase 3 trials of ADT, with or without potent androgen receptor inhibition in this curative-intent setting.

Addition of six months of oral daily enzalutamide to standard salvage RT and ADT is safe and may improve PCa remission rates at two and three years.

Robotic Assisted Radical Prostatectomy Associated With Decreased Persistent Postoperative Opioid Use

Shkolyar E, Shih I-F, L Yi, Wong J, Liao JC

J Endourol. 17 February 2020; Epub ahead of print

Minimally invasive surgery offers reduced pain and opioid use postoperatively compared to open surgery, but large-scale comparative studies are lacking. We assessed the incidence of persistent opioid use after open and robotic-assisted radical prostatectomy (RP).

We performed a retrospective claims database cohort study of opioid-naive (i.e., no opioid prescriptions 30-180 days before index surgery) adult males who underwent RP for prostate cancer from July 2013-June 2017. For patients who filled a perioperative opioid prescription (30 days before to 14 days after surgery), we calculated the incidence of new persistent postoperative opioid use (one or more prescription 90-180 days after surgery). Multivariable logistic regression was performed to investigate the association between surgical approach, patient risk factors and persistent opioid use.

12,278 RP patients filled an opioid prescription perioperatively (1,510 [12%] open, 10,768 [88%] robotic-assisted). Of these, 846 (6.9%) patients continued to fill opioid prescription(s) 90-180 days after surgery. Patients undergoing robotic-assisted were 35% less likely to develop new persistent opioid use compared to those undergoing open RP (6.5 vs. 9.7%; adjusted odds-ratio [OR] 0.65; 95% confidence interval [CI] 0.54-0.79). Other independent risk factors included living in the southern, western or north-central United States, preoperative comorbidity and tobacco use.

Approximately 6.9% of opioid-naive patients continued to fill opioid prescriptions 90 days after RP. The risk of persistent opioid use was significantly lower among patients undergoing a robotic-assisted vs. open approach. Further efforts are needed to develop postoperative opioid prescription protocols for patients undergoing RP.
I was going to write about a fabulous clinical study of prostate cancer (PCa) patients losing weight on a low-carbohydrate diet, but that story can wait until next month or so. The reality is this COVID-19 thing is getting serious and, having spent 30+ years in epidemiology and having published some medical/research papers on parasites, colds, flu etc., I feel compelled to do my thing here (aka give my one cent of advice).

I often say that heart healthy = prostate healthy but what I am also implying with this statement is simply that heart healthy = immune healthy. Over time it is interesting how much research has been conducted showing virtually anything reducing the risk of cardiovascular disease (CVD) also appears to enhance the immune response to many infectious agents, whether preventing them, or potentially enhancing the impact of conventional treatment.

Interestingly, this also applies to responding better to adult prevention vaccines! Yes, it appears you can make a vaccine or human immune system work even better by being more heart healthy. For example, lifestyle changes from diet, exercise, better sleep, weight loss, stress reduction, moderation or no alcohol, quitting tobacco, etc. Every time I research something that reduces the risk of CVD, including normalizing blood pressure, sugar, cholesterol, it also appears to improve your immune response! Now, of course, I cannot claim that this will also fight COVID-19, but it does appear that it could make someone less vulnerable. But the good news is that, if I am wrong, I am still just giving you advice to help you live better and longer.

I do not like COVID-19! I also do not like it when some “experts” tell us not to worry about it right now and place it in perspective?! This sounds good, but how do you give perspective on something that has never really happened before in our lifetime. Shortly, and with more research, we will get the right perspective. I want honest and tangible advice that in the worst-case scenario makes me healthier and in the best-case scenario makes me healthy! I want the win-win and we can have that.

Cancelling meetings? Absolutely! Washing hands with plain soap and water, social distancing, hand sanitizer (with at least 60% alcohol), no handshakes, no fist bumps or elbow touching, wiping down surfaces, trashing the Kleenex asap after using it, and mouth, nose, and eyes should receive no attention from your fingers, monitoring your overall health, being completely compliant with your medications... (not enough space here for all my tips, but you get the idea).

When dealing with public health issue(s), I try to impose rules such as “when in doubt eliminate the doubt” or “if the worst-case scenario is far worse than the best-case scenario then you know what to do.” This is partly why we did not hesitate to cancel in-person audience attendance for a recent national patient meeting. In other words, we’re learning in real time about COVID-19, and no one knows exactly what it is specifically or how we will conquer it yet, but we do know one way to reach optimal immune health is to aim for optimal cardiovascular health. As we get older, we experience “immunosenescence” – progressively reduced immune health. To level the playing field we need to know Heart healthy = immune healthy.

I wish you the best of health! Of course I am optimistic we’ll eventually corral this damn thing, but for now let’s try to achieve optimum cardiovascular health. I look forward to modern-day science kicking this virus in the gluteus maximus!

Reference:

The Cost of Bottling it Up – Emotion Suppression as a Mediator in the Relationship between Anger and Depression Among Men with Prostate Cancer

Rice SM, Kealy D, Ogrodniczuk JS, Seidler ZE, Denehy L, Oliffe JL
Cancer Manag Res. 11 February 2020; Epub

Prostate cancer (PCa) is a risk factor for major depression. Recent psycho-oncology research suggests a potential role for male-specific mood-related symptoms in this relationship. Gender socialization experiences may reinforce men’s anger and emotion suppression responses in times of distress, and these two responses may involve pathways to, and maintenance of depression in PCa. Data were collected online from 100 men with a self-reported PCa diagnosis (mean age 64.8 years). Respondents provided information about diagnosis and treatment, in addition to current experiences of major depression and male-specific externalizing symptoms. PCa diagnosis in the last 12 months occurred for 35.4% of the sample. Elevated major depression symptoms were observed for 49% of respondents, with 14% endorsing past two-week suicide ideation. Parallel mediation analysis (99% CIs) controlling for prostatectomy and active surveillance (AS) indicated men’s emotion suppression mediated the relationship between anger and depression symptoms ($R^2=0.580$). Trichotomized emotion suppression scores with control variables yielded a large multivariate effect ($p<0.001$, partial $\eta^2=0.199$). Univariate, moderate-sized effects were seen for emotion suppression comparisons for symptoms of depressed mood and sleep disturbance, and a large effect (Continued on page 6)
Thumbs Down for Prostate Cancer Focal Therapy (Continued from page 1)

years, as more data accumulate... the vote may completely turn around as there is more clear data about this,” he added. Other members of the panel were less sanguine about the treatment or its future.

“I see a lot of men for second opinions,” said Patrick Walsh, MD, of Johns Hopkins Medical Center in Baltimore. “I’m very confident in low-risk disease with offering active surveillance (AS) because of the data we have at Hopkins. For over 18 years and 1,800 men with low-risk disease, 0.6% developed metastases and 0.1% died.”

Musing about the meaning of statistical significance, Walsh quoted author Gertrude Stein: “A difference, to be a difference, must make a difference.”

“I think most of these men [treated with TOOKAD] won’t be told that at two years half of them will still have cancer and in 28% it will be progressing... I think there are many doctors out there who are in business, and this will be an opportunity that will be misused,” said Walsh.

Daniel Song, MD, also of Johns Hopkins, agreed that focal therapy could definitely be misused. Still, he counted himself as one of those on the fence: “I could see how this would be beneficial to some patients, but not the ones in this study, as demonstrated here,” he said.

Maha Hussain, MD, of Northwestern University Feinberg School of Medicine suggested focal treatments such as TOOKAD may actually add to patients’ confusion about options for low-risk PCa, including AS: “How do you justify saying to men, ‘I don’t think you really need a treatment and we really should just watch you, but by the way we’re going to give you a sprinkle of treatment?’

Discussion of treatment pros and cons centered on the primary evidence supporting approval application, a phase III randomized, open-label trial of TOOKAD vs. AS in 413 men with newly diagnosed, localized, low-risk PCa.

The trial had two coprimary endpoints and met both:

- Absence of PCa at 24 months (49.0 vs. 13.5%, P <0.001)
- Freedom from progression from low- to intermediate- or high-risk disease (28.2 vs. 58.5%, P <0.001)

An FDA staff analysis cited several issues with the trial design and data. With regard to endpoint #1, FDA staff noted that its “clinical meaningfulness in early-stage PCa is unknown.” The second endpoint “was never used as an endpoint for regulatory approval, partially based on lack of validated data.”

The report also questioned the reliability of biopsies obtained after TOOKAD treatment, which causes scarring. With regard to toxicity, the report noted that men on AS did not encounter treatment-related adverse events until disease progression, whereas the TOOKAD group was exposed to potential toxicities at the time of treatment.

Additionally, FDA staff noted a substantial disparity in toxicity reporting for men in AS who underwent definitive therapy as compared with men randomized to TOOKAD.

Finally, Steba, with input from the FDA, designed another trial comparing TOOKAD and AS with a primary endpoint of objective progression at 30 months. The staff report questioned whether the treatment should be deferred until completion of that trial—which, according to its Clinicaltrials.gov listing, is estimated to be in 2030.

The report concluded with the question: “Do the results of PCM301 represent a favorable benefit/risk profile for TOOKAD in patients with low-risk early-stage PCa?”

Steba’s briefing document for the committee emphasized that TOOKAD fills a treatment void: “AS candefer the need for radical therapy, but only temporarily for many men. These patients need alternatives that target the cancer area and preserve the surrounding tissues and, consequently, quality of life.”

“In the pivotal study, TOOKAD VTP increases the probability of a negative prostate biopsy 24 months post-treatment vs. AS and a statistically significant reduction in local disease progression,” the report stated.

“Multiple sensitivity analyses confirmed the robustness of the time to progression endpoint. Importantly, TOOKAD VTP treatment also reduced the rate of conversion to radical therapy vs. AS, which predicts reduced morbidities of radical therapy and shows a clear benefit for patients.”

MedPage Today
26 February 2020

Sunitinib in Combination with Docetaxel and Prednisone in Chemotherapy Naive Patients with Metastatic Castration Resistant Prostate Cancer: A Phase 1/2 Clinical Trial


Ann Oncol. 04 December 2019; Epub

This phase 1/2 study assessed sunitinib combined with docetaxel and prednisone in men with chemotherapy-naive metastatic, castration-resistant prostate cancer (mCRPC).

To determine the recommended phase 2 dose (RP2D), 25 men in four dose escalation cohorts received three-week cycles of sunitinib (two weeks on, one week off), docetaxel and prednisone, preceded by a four-week sunitinib 50 mg/day lead-in. RP2D was evaluated in 55 additional men. The primary end point was PSA response rate.

One phase 1 dose-limiting toxicity occurred (grade 3 hyponatremia). The RP2D was sunitinib 37.5 mg/day, docetaxel 75 mg/m² (every three weeks) and prednisone 5 mg twice a day. During phase 2, confirmed PSA responses occurred in 31 men [56.4% (95% confidence interval [CI], 42.3-69.7)]. Median time to PSA progression was 9.8 months. Forty-one men (75%) were treated more than three months, 12 (22%) completed the study (16 cycles) and 43 (78%) discontinued (36% for disease progression and 27% due to adverse events). The most frequent treatment-related grade 3/4 adverse events were neutropenia (53%); 15% febrile [with fever] and fatigue/asthenia (16%).

Among 33 assessable men,

(Continued on page 8)
Hypofractionated Radiotherapy for Prostate Cancer Stands the Test of Time (Continued from page 1)

David P. Dearnaley, MB BCh, MD, of the Royal Marsden NHS Foundation Trust, London, reported the eight-year results at the 2020 Genitourinary Cancers Symposium (GuS) held in San Francisco.

Study Details

“At a median follow-up of 9.3 years, the eight-year rate of freedom from biochemical failure (defined by Phoenix consensus guidelines) or clinical failure (cancer recurrence) was 80.6, 83.7 and 78.5% with 74, 60 and 57 Gy,” Dr. Dearnaley reported.

Analyses confirmed noninferiority of the 60-Gy regimen (HR, 0.85; 95% confidence interval [CI], 0.72-1.01; P=0.11), but not the 57-Gy regimen (HR, 1.17; 95% CI, 1.00-1.36; P=0.10), as the upper bound of the CI crossed the predefined 1.21 boundary for noninferiority.

The three regimens yielded a similarly high rate of freedom from metastases, at about 95% in each arm. “Because there is an 8:1 ratio of non-PCa deaths to PCa deaths, you would have to postulate something other than PCa being affected by the RT fractionation,” he said.

On central pathology review, nearly a fifth of evaluated trial patients had high-risk disease. Dr. Dearnaley stated that he would rather not do a specific high-risk subgroup analysis, expressing concern about performing too many subgroup analyses.

There were no differences between groups on rates of Radiation Therapy Oncology Group toxicity at five years, with grade 2 or worse bowel and bladder toxicity each seen in about 2% of men. There were no significant differences in rates of patient-reported “moderate or big” bowel bother (~5-8%) and urinary bother (~7-9%). For all regimens, bowel and urinary symptoms remained stable from two-five years.

These updated findings “support the continued use of 60 Gy in 20 fractions as the standard of care,” Dr. Dearnaley said. “When the math is run to permit comparison, efficacy findings of the CHHiP trial show ‘amazing agreement’ with those of the similar multinational PROFIT trial,” he noted.

The absolute advantage in the failure-free rate of 3.1% and the overall survival rate of 2.7% for the 60-Gy regimen in CHHiP generated interest among attendees. However, Dr. Dearnaley acknowledged that these differences are not statistically significant.

“This CHHiP update is fantastic,” said session cochair Paul L. Nguyen, MD, of the Dana-Farber Cancer Institute in Boston. “This trial is the only noninferiority hypofractionation trial in PCa that includes a sizable share of patients at high risk for poor outcomes, a population for whom efficacy of this strategy is of particular interest,” he noted.

“That’s always been a question,” he said. “The majority of the data from the noninferiority trials is for the low- and intermediate-risk patients. So, it really would be interesting to learn whatever we can about high-risk patients from this trial.”

Presented at the 2020 Annual GUcS; abstract 82
Medscape Oncology
24 February 2020

Sustained Benefit of Apalutamide in mCRPC (Continued from page 1)

who are contemplating various treatment options.”

Study Details

Among the 277 men experiencing progression on their trial therapy and going on to receive a life-prolonging subsequent therapy, about 30% later received a new hormonal therapy – abiraterone or enzalutamide – and 35% subsequently received a taxane – docetaxel or cabazitaxel.

“Overall, PFS2 was significantly better for men initially randomized to apalutamide, vs. counterparts initially randomized to placebo (hazard ratio [HR] for events, 0.66; P=0.0026, a statistically significant difference),” Dr. Agarwal reported at the GuCS symposium.

In stratified analyses, PFS2 was also significantly better with initial apalutamide vs. placebo whether patients went on to receive a new hormonal therapy (HR for events, 0.684; P=0.0326) or taxane chemotherapy (HR for events, 0.634; P=0.0062, both are statistically significant differences). Median values were not reached.

Some Cavets

As only about a fifth of men experienced PFS2 events, “these findings need to be interpreted with some caution,” said invited discussant Dana E. Rathkopf, MD, a genitourinary medical oncologist at Memorial Sloan Kettering Cancer Center in New York.

“Another caveat is that the analyzed cohort were poor responders, who had experienced progression at a median of roughly 12 months whether on apalutamide or placebo,” she noted. “If the patients were all on treatment for about 12 months, it does make me wonder why apalutamide patients responded better than placebo patients to a second hormonal therapy, because you might think that in the setting of poor response to upfront apalutamide, these patients may develop some type of intrinsic resistance that would suggest they would not respond to a second-line androgen receptor inhibitor vs. to a taxane.

“Patients in TITAN were stratified on prior receipt of docetaxel before undergoing randomization. But simply by chance, among those receiving subsequent hormonal therapy, a larger share of those initially treated with apalutamide than of those initially treated with placebo had received the taxane (33% vs. 16%), which may have influenced outcomes,” Dr. Rathkopf added.

“Further maturation of the data will tell us more,” she concluded. “But clearly, apalutamide in both the SPARTAN and TITAN trials improved PFS2 relative to placebo, and this begs the question of how we can better select treatment using predictive markers.”

“The analysis was performed post hoc, and the subsequent therapy was left up to the treating clinicians,” stated Dr. Agarwal, professor of medicine and director of the genitourinary oncology program at the Huntsman Cancer Institute, University of Utah in Salt Lake City.

“A small number of events on subsequent therapy and the nonrandomized treatment decision preclude determination of best subsequent therapy based on these data,” he concluded.

Presented at the 2020 annual GUcS; abstract 82
Medscape Oncology
24 February 2020
Lengthening the interval between prostate cancer (PCa) screenings for men with low PSA levels was, unsurprisingly, predicted to modestly reduce the risk of overdiagnosis, according to a modeling study by Dutch and American investigators.

But the results also showed that a longer screening interval would eventually lead to higher mortality rates from the disease compared with screening every two years, reported Eveline A.M. Heijnsdijk, PhD, of Erasmus MC University Medical Center in Rotterdam, The Netherlands, and colleagues online in the *Journal of the National Cancer Institute*.

Compared with biennial PSA testing from ages 45-69, the group calculated that if men with PSA levels <1.0 ng/mL at age 45 were screened every eight years instead of every two years, there would be approximately 47% fewer tests done and approximately 1-2% fewer overdiagnoses. However, approximately 3-4% fewer lives would be saved using PSA-stratified screening approach.

Another model where, instead, screening was stopped altogether at age 60 if levels were below 1.0 ng/mL was estimated to result in approximately 5.5-24.0% fewer overdiagnoses but 5.0-13.1% more deaths compared with continued biennial PSA screening until age 69.

“Less intensive PSA screening in men with low PSA levels can substantially reduce the testing burden. Both models project that stratifying screening by PSA level is expected to reduce overdiagnosis by a modest amount while preserving the majority of the benefit of screening,” the team wrote.

Asked for his opinion of the results, William Catalona, MD, of Northwestern University Feinberg School of Medicine in Chicago said he disagreed with lengthening PSA screening intervals.

“In my practice, I now see daily the sad effects of men who have had a hiatus in their PSA testing or have not been tested because their doctors have told them that PSA testing caused more harm than good,” he stated.

“I believe that suggesting less PSA testing is desirable could compromise many men.”

For the study, Heijnsdijk and co-investigators used different predictive models – the Erasmus University Medical Center-Microsimulation Screening Analysis (E-MISCAN) and the Fred Hutchinson Cancer Research Center (FHCRC) model – to arrive at their calculations.

“Using the calibrated models, we simulated cohorts of men in the U.S., age 45 or 50 in 2017 and followed until age 85,” the team explained. The calculations were based on these screening strategies:

- **Screening from ages 45 to 69 at two-year intervals**
- **Lengthening screening to eight years for men with a PSA level <1.0 ng/mL at age 45, but decreasing it again to two years if the levels rose to >1.0 ng/mL on a later screening**
- **Stopping screening completely if the PSA level remained at less than 1.0 ng/mL at age 60 and older**
- **Using a combination of the last two strategies**

Using the combination strategy, the E-MISCAN model projected a 52.2% reduction in the number of screening tests carried out, a 24.4% reduction in overdiagnosis, and a 14.8% reduction in the number of lives saved. The FHCRC model projected a 51.1% reduction in the number of screening tests done, a 5.7% reduction in overdiagnosis, and a 7.5% reduction in lives saved.

Compared with no PSA screening, the two models “projected that screening 10,000 men ages 45-69 biennially would require more than 110,000 screenings, yield 277 (E-MISCAN) to 348 (FHCRC) overdiagnoses, save 110 (E-MISCAN) to 160 (FHCRC) lives and gain 921 (E-MISCAN) to 1,312 (FHCRC) life-years,” the authors say.

The predicted reduction in PCa-specific mortality was 38.6% for the E-MISCAN vs. 53.3% for the FHCRC model, compared to a no-screening model. Both models predicted that discontinuing screening at age 60 would reduce overdiagnoses by approximately 80%, but about 50% more lives would be lost vs. a policy where men are screened until age 69.

“The models agree qualitatively across all settings that PSA-stratified strategies will lead to modest reductions in both overdiagnoses and lives saved,” Heijnsdijk and co-authors stated. “Depending on how these harms and benefits are valued, our results confirm that PSA-based stratification could lead to more efficient use of the PSA test in early detection of PCa,” the team concluded.

Catalona agreed that results support a risk-stratified approach to PCa screening.

“However, statistical modeling studies have limitations in accurately reflecting real-world scenarios, and statistical modeling are usually not considered sufficiently rigorous to support hard recommendations for clinical adoption,” he said.

Catalona also noted that the current benefit-harm analysis does not include the frequency of metastases at diagnosis, which is determined only by early detection and, said the authors “fail to consider preventing suffering and treatment of metastatic disease, which is a burden to patients and their families.”

In addition, Catalona said prolonging screening intervals >two years delays the diagnosis of the most aggressive cancers. “This makes a recommendation of lengthening screening intervals to four or eight years or completely discontinuing screening when PSA is below 1.0 ng/mL at the age of 60 particularly concerning,” he said.

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**Bottling It Up**

*(Continued from page 3)*

observed for guilt-proneness. Findings highlight the salience of anger in the experience of depression symptoms for men with PCa. The mediating role of emotion suppression which, in turn, was strongly linked to feelings of guilt, suggests potential assessment and intervention targets. Future work should examine the role of androgen deprivation therapy and other treatments including AS on the relationship between anger and depression in men with PCa. Consideration of interventions focused on emotion processing skills in psychosocial settings may help reduce men’s reliance on emotion suppression as a strategy for coping with feelings of anger or guilt in the context of PCa.
The days of poke and hope are over! For decades prostate biopsies have been performed in a random, systematic fashion. An ultrasound probe is inserted into the patient’s rectum and an image of the shape of the prostate gland is obtained. Random, systematic cores are taken out at the apex level (bottom), the mid-gland level and the base (top). This is conventionally known as transrectal ultrasound guided biopsy or TRUS biopsy, and has been the standard for decades. This procedure is usually performed in an outpatient setting.

With the advent of multiparametric MRI, we are now able to look at detailed images of the prostate gland and aim the biopsy needle toward a specific target rather than systematically sampling 10, 12 or 18 cores or more. MRI allows us to see anatomic and morphologic features as well as functional information like perfusion, or blood flow and diffusion, movement of water molecules between cells. These functional sequences add great value and improve diagnostic performance.

The more likely malignancy is present – there is an inverse, linear relationship between ADC value and tumor aggressiveness. This relationship has been well published in the radiology and urology literature. It is important to note that there are other things besides cancer that can cause a low ADC, for example infection or inflammation.

The best part about MRI is that we are able to aim at a target within a target; in other words, if a lesion has one particular area that looks most suspicious, we can take aim at that part of the tumor with pinpoint precision. The benefit is more accurate Gleason scoring and better tissue-based genomics. If a random biopsy is performed, there can be misclassification of disease, especially if the tumor is far toward the front of the prostate gland, which can be missed with TRUS biopsy.

For the patient, the procedure is very straightforward. He lies on the MRI scan table on his stomach. A needle guide smaller than an adult’s index finger is inserted into the rectum. The needle guide functions two ways: it is both a receptacle for instruments to be inserted and it functions as a fiducial marker. Our specialized computer software allows us to see the needle guide and its relationship to the target area. The software gives us coordinates that allow us to aim at the area of interest with a high degree of accuracy. We can angle left, right, front, back and insert or retract the device to aim squarely at the target. Once the needle has been deployed, the technologist takes an image of it in the fixed position. We have our pathologist include this image in our report so that it is indisputable where the tissue came from. The procedure takes only about a half an hour and does not require anesthesia. Numbing gel is used to ease any possible discomfort and patients tolerate the procedure extremely well. There is also an extremely low risk of infection on the order of 0.6%, which we presented at the annual American Urological Association meeting in San Francisco.

Once the biopsy specimens are collected, they are sent to a specialized laboratory for the pathologist to evaluate them and generate a report of findings. Our pathologist is specifically trained in prostate cancer evaluation. In many cases we send the specimens to another laboratory for genomic testing. This test looks at 22 genes known to be associated with prostate cancer. The report will designate the patient as low-, intermediate- or high-risk as it relates to potential for metastasis, or spread of cancer outside the prostate gland to lymph nodes or skeletal structures. This information can be a very helpful piece of a complicated jigsaw puzzle.

Another important piece of the puzzle is PSA density. This is the patient’s PSA divided by their prostate gland volume. This helpful prognostic indicator combined with imaging findings and genomics can be very helpful. To use an example: if one man has a prostate the size of an apricot and another man has a prostate the size of a grapefruit and they both possess a PSA level of 4 ng/mL, the one with the smaller gland will have a higher PSA density than the man with the larger gland. MRI allows us to measure the prostate gland in order to accurately calculate PSA density.

The functional MRI sequences also allow us to monitor response to treatment over time so we could tell if a patient is responding well to whichever therapy they choose. Even if they are on active surveillance or watchful waiting, the MRI allows us to monitor the patient and keep him safe. In the United Kingdom and the European Union guidelines have been published mandating MRI prior to biopsy and recently the American Urological Association published their policy statement agreeing with those guidelines and implementing it in the United States. We tell our patients to never allow anyone to put a finger, a needle or a scalpel anywhere near your prostate gland unless they have done an MRI first. If you want more information about MRI targeted biopsy you can visit our website at www.halodx.com.
The adrenal-permissive HSD3B1 genotype is associated with worse clinical outcomes in men with metastatic castration-sensitive prostate cancer (mCSPC), according to an analysis of data from a clinical trial.

Carrying one or more copies of the allele is associated with a shorter interval from androgen-deprivation therapy (ADT) “to castration-resistant prostate cancer (CRPC), as well as shorter overall survival, in men with low-volume metastatic prostate cancer (PCa),” Dr. Nima Sharifi of Cleveland Clinic, in Ohio, told Reuters Health.

The HSD3B1(1245C) adrenal-permissive allele encodes a stable enzyme that allows for permissive allele inheritance of the adrenal-permissive allele to worse clinical endpoints.

Dr. Sharifi and colleagues analyzed outcomes in white men enrolled in the E3805 CHAARTED trial according to HSD3B1 genotype, hypothesizing that accentuated extragonadal DHT synthesis associated with the adrenal-permissive allele would be associated with more rapid development of CRPC and lower overall survival.

Among the 475 white men included in the study, 56.8% had the adrenal-permissive genotype, vs. only 13.5% of nonwhite men. Most men (N=301) had high-volume disease, and 174 had low-volume disease.

Freedom from CRPC at two years was significantly lower in men with low-volume disease with the adrenal-permissive genotype (51.0%) vs. the adrenal-restrictive genotype (70.5%), the researchers reported online in JAMA Oncology. In multivariable analysis, the adrenal-permissive genotype was associated with 89% higher risk of CRPC. In contrast, there was no significant difference based on HSD3B1 genotype in freedom from CRPC at two years in men with high-volume disease.

Overall survival at five years was significantly worse in men with low-volume disease who had the adrenal-permissive genotype (57.5%) vs. those with the adrenal-restrictive genotype (70.8%). But there was no significant difference in overall survival by genotype in men with high-volume disease.

Men with low-volume disease did not benefit significantly from docetaxel, but men with high-volume disease did benefit, regardless of HSD3B1 genotype.

“We need additional information before routine testing is suggested,” Dr. Sharifi said. “Broadly, HSD3B1 genotyping tells us how much an individual man’s tumor is dependent on extragonadal (or adrenal) androgens. Additional analyses that are planned in other clinical trials will help us determine how best to use this information for clinical management.”

Reuters Health Information
26 February 2020

Sunitinib + Chemo
(Continued from page 4)
14 (42.4%) had confirmed partial response. Median progression-free and overall survival rates were 12.6 and 21.7 months, respectively.
This combination was moderately well tolerated, with promising response rate and survival benefit, justifying further investigation in men with mCRPC.

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Hot SHEET – APRIL 2020
**Between the Sheets...**

April 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. 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)

**QUESTION FROM PROSTATE CANCER SURVIVOR:**

I have chosen to go on active surveillance because I have low risk prostate cancer (diagnosed 6 months ago) and I do not want to deal with the prospect of sexual changes after surgery or radiation. I am recently divorced and sex is important to me, especially now that I am single (and looking!). I have noticed in the past few months that my erections are not as rigid as they once were. Could this have something to do with being on active surveillance? I am 61 years old and have never had this problem before.

**RESPONSE FROM DR. ANNE KATZ:**

It is said that the brain is the biggest sex organ and there is truth to that. Erections are not purely mechanical or hydraulic and your mood and general emotional status can and do affect multiple aspects of sexual functioning. You have experienced a LOT of change recently – the diagnosis of prostate cancer, making a treatment decision, divorce, perhaps moving to a new home or adapting to living alone in your old home... This is a lot of change and any and all of these may be involved in how your penis is acting and reacting. A diagnosis of prostate cancer itself and the very real potential for the sexual side effects of treatment cut to the very heart of masculinity and masculine self-image. Add to that the challenges of projecting the challenges of establishing a new romantic or sexual partner and your erectile functioning is going to undergo some change. Add to that the fact that many men experience changes in erections as they age and in your 60s you may start to gain weight leading to medical issues such as early cardiovascular disease and diabetes.

There is almost no research on the sexual side effects of being on active surveillance but there are certainly studies that show that men experience anxiety when following this treatment strategy. This does not mean you should give up on it! But think about how you might be feeling, even subconsciously, about the regular monitoring of your PSA and perhaps repeated biopsies and what messages you might be hearing from your family and/or friends about “doing nothing” or “not being treated”. All of these potentially add stress that can lead to anxiety and second guessing your treatment decision.

In addition, failing to achieve or maintain an erection can become a self-fulfilling prophecy – or cause performance anxiety – so talk to your urologist or primary care provider about using one of the oral medications that can act as a ‘safety net’ and provide you with both confidence and assistance with your erectile function. A general check-up of your blood pressure, cholesterol and blood glucose is also warranted – the penis is the ‘canary in the coalmine’ for general health as changes in erections may be an early warning sign of underlying cardiac health.

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](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

Or mail your letter to:
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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).

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.

Breaking Down Barriers to Treatment – Literally

In the past few years, several new treatment options have become available to patients with advanced prostate cancer. Radionuclide therapy is a new class of treatments which uses a hybrid “targeting” molecule to bind to a target protein on prostate cancer cells and a radioactive “killing” molecule to destroy the cell. One such target is called Prostate-Specific Membrane Antigen (PSMA). PSMA-targeted radionuclide therapy is being tested in a Phase 3 clinical trial. However, these therapies do not work in all patients, and more options are needed.

One barrier to effectively delivering treatment surrounds the tumor itself: the stroma (coming from the Greek for “layer” or “bed covering”). The tumor stroma is composed of many non-tumor cells that exist in normal tissues and play a role in wound-healing processes. A team led by PCF-funded UCLA investigators (Dr. Johannes Czernin, Dr. Jeremie Calais, Dr. Christine Mona and Dr. Katharina Lueckerath), are taking an innovative approach to treatment by literally breaking down this “wall.”

A key component of the stroma are fibroblasts, a cell type that are commonly recruited into tumors. These “cancer-associated fibroblasts” are highly supportive of tumor growth and metastasis via expression of proteins including fibroblast activation protein (FAP). FAP is expressed in the stroma of many tumor types to various degrees, including in 20% of primary prostate cancers. A compound that specifically binds to FAP may be able to identify, target, and ultimately destroy tumors.

Researchers from the University of Heidelberg in Germany have developed small molecule inhibitors of FAP (FAPi-46). These small molecules can be labeled with a diagnostic radioactive molecule that will light up in a PET scan, thus making the FAPi useful for identifying which cancers express FAP. FAPi-46 can also be labeled with a therapeutic radioactive molecule. When the therapeutic FAPi binds to stroma fibroblasts it may damage stroma function and damage the barrier around the actual tumor cells. From there, chemotherapy or another radioactive drug aimed at the now-exposed tumor cells could be deployed.

What does this mean for patients? Although this novel approach is still several years away from clinical care, research actively continues. The UCLA team has initiated clinical studies testing radiolabeled FAPi as a PET imaging agent in patients with different cancer types. The team is also testing FAP-targeted radiotherapy in prostate cancer mouse models. The toxicity profile in small animals has been favorable.

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