INSIDE THIS ISSUE

PSA – Here’s Your Competition for Prostate Cancer Screening
Hit & Miss in Castration-Resistant Prostate Cancer Treatment
CCR Score Could Offer ADT-Free Path in High-Risk Prostate Cancer
ED Is a Transient Complication of Prostate Biopsy: A Systematic
MRI-Guided Prostate Biopsy Prevalts in PRECISE Trial
Dr. Moyad’s No Bogus Science: “Move More = Sleep Better + Dogs?!”
RT’s Role in Metastatic PCa Clarified
Radionuclide Treatment Wins in Third-Line Treatment of mCRPC
Decipher Test May Guide Post-Op Treatment in Prostate Cancer
Combination Treatment Disappoints in Metastatic CRPC

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PSA – Here’s Your Competition for Prostate Cancer Screening
Imaging Looks Like a Winner in New Study

MRI screening detected more clinically significant prostate cancers (PCa) than did PSA testing alone in the IP1-PROSTAGRAM study – without increasing overdiagnosis of clinically insignificant cancers with the imaging approach.

The prospective, population-based study invited 2,034 men from 7 primary care practices and 2 imaging centers in Great Britain to undergo PCa screening. Of those invited, 408 men underwent screening MRI, ultrasoundography (US), and PSA test; 310 had the tests on the same day. Serum PSA level of 3 ng/mL was the cutoff for positive results.

“More men had positive MRI scores (3-5 on a 5-point scale of suspicion) than had positive PSA test results (17.7% vs. 9.9%; P <0.001),” reported David Eldred-Evans, MBBS, of Imperial College London, and colleagues.

(Continued on page 4)

CCR Score Could Offer ADT Free Path in Higher-Risk Prostate Cancer

A prognostic risk estimator that incorporates genomic data and clinical factors could allow for the elimination of androgen deprivation therapy (ADT) in some men with intermediate- or high-risk PCa post-therapy radiation therapy (RT), according to the findings presented at the 2021 virtual Genitourinary Cancers Symposium (GuCS).

“In a retrospective study of 741 evaluable men receiving dose-escalated RT, those with a clinical cell-cycle risk (CCR) score below a 2.112 threshold had a 10-year risk of distant metastasis of 4.1%, regardless of National Comprehensive Cancer Network (NCCN) risk group, while those above the threshold had a 10-year risk of 25.3%,” reported Jonathan Tward, MD, PhD, of the University of Utah in Salt Lake City.

“In those with the lower score, differences were negligible based on receipt of RT alone (4.2%), or RT plus ADT (3.9%). Many studies have shown that adding ADT decreases risk of metastasis in men with PCa,” said Tward.

“Nevertheless, this clear relative benefit may become clinically questionable when the baseline risk of metastasis in any population or individual is low.”

CCR score combines the cell cycle progression (CCP) score, using the Prolapris test, with the UCSF Cancer of the Prostate Risk Assessment (CAPRA) score – which factors in age, PSA levels, Gleason score, T stage, and percentage of positive cores on biopsy.

Prior research had established a CCR score of 2.112 as a cutoff where men with in-

(Continued on page 6)
Erectile Dysfunction is a Transient Complication of Prostate Biopsy
A Systematic Review and Meta-Analysis


J Urol 205: 664-670, 2021

Purpose: Because the association between erectile dysfunction (ED) and prostate biopsy is variable in the available literature, we sought to perform a systematic review and meta-analysis of sexual dysfunction in males within 6 months of prostate biopsy.

Materials and Methods: We conducted a systematic literature search in 4 databases: MEDLINE® (via PubMed®), Embase® (via Ovid®), Web of Science™ and the Cochrane Library. We included studies focused on sexual dysfunction in men of all age groups undergoing transrectal or transperineal prostate biopsy for suspicion of prostate cancer (PCa). We included studies with International Index of Erectile Function-5 (IIEF-5) scores pre-biopsy and post-biopsy at 1, 3 or 6 months. We performed an effect size meta-analysis comparing baseline IIEF-5 scores with post-biopsy IIEF-5 scores.

Results: We identified 9 studies that met our inclusion criteria, of which 6 examined transrectal prostate biopsy, 2 examined transperineal prostate biopsy and 1 examined both. At 1 month after biopsy, the mean IIEF-5 score decreased by approximately 2.2 points as determined by the effect size (-0.43, p=0.002). However, at 3 and 6 months after biopsy, there was no difference compared to baseline (effect size -0.08, p=0.52 and effect size -0.11, p=0.18, respectively). An exploratory subgroup analysis examining transrectal prostate biopsy at 3 months showed a statistically significantly lower mean IIEF-5 score compared to baseline (p=0.047), corresponding to an approximately 1.25-point decrease in IIEF-5.

Conclusions: Prostate biopsy does cause a mild, transient decrease in average IIEF-5 scores at 1-month post-biopsy. However, this resolves at 3 months on average, and average IIEF-5 remains at baseline at 6 months post-biopsy.

Here’s welcome news for men of a certain age: new results support a less invasive approach to investigations for suspicion of prostate cancer (PCa). An approach using MRI of the prostate followed by targeted biopsy (TB) in men with images suggesting a high risk beat the conventional approach of using transrectal ultrasound (TRUS)-guided 12-core systematic biopsy. Results come from the randomized phase 3 PRECISE trial and were published online in JAMA Oncology on 4 February 2021.

“The trial showed that, by taking an imaging-first strategy, you could reduce the number of men needing a biopsy by about 40% and actually find more significant cancer (35% vs. 30%) and reduce the diagnosis of grade group 1 cancers that we don’t want to find by more than half,” lead author Laurence Klotz, CM, MD, from Sunnybrook Health Sciences Centre in Toronto, Canada, said in an interview with Medscape Medical News. The PRECISION trial had already provided “compelling evidence in favor of MRI and targeted biopsy,” notes Olivier Rouvière, MD, PhD, from the University of Lyon, Lyon, France, writing an accompanying editorial. But he argues that it was worth duplicating the trial, as “it must not be forgotten that in science, testing the robustness of an effect and the factors influencing it are as important as demonstrating this effect in the first place.

“Results from both trials suggest that, instead of replacing TRUS biopsy entirely, MRI results could be used to guide men to the appropriate diagnostic pathway,” Rouvière commented.

“Using only MRI findings to decide which men should undergo biopsy is probably insufficient,” he adds. “Most likely, MRI findings will be used in conjunction with oth-

(Continued on page 7)
Okay, I wanted to talk about that new study of dogs capable of detecting PCa, but I thought I might be BARKING up the wrong tree since I wrote about this subject long ago. Ergo, I am going to skip that study, but since dogs might be able to detect a variety of cancers... well it just shows you that anything is PAW(s)ible. No laugh? Man, this is a RUFF-RUFF crowd, so please FUR-give me if you do not like my puns, but maybe you are the one that needs a new LEASH on life?

So, let us talk about insomnia or sleep issues. There are so many pills for sleep that I’ve lost count, especially over the counter (OTC). Some of the more popular OTC brands are simply Benadryl (diphenhydramine) in disguise. Many prescription options have some efficacy, but they also have some serious cost and safety issues. Cognitive behavioral therapy (CBT) is a great option that does not get enough attention, but this can also be costly, and some newer online programs have appeared that are far cheaper.

However, what happened to simple regular exercise of any type as we get older?

A recent randomized study of 320 adults, average age of 67 years, and with chronic insomnia aimed to determine if tai chi vs. conventional exercise (60-minute small group sessions 3 times a week) vs. a control group over 12 weeks could be effective. It turns out tai chi OR conventional exercise (simple stretching and walking) worked equally well vs. the control group, and the diverse positive benefits were maintained “24 months post-intervention!” Wow! Wow spelled backwards!

A randomized 2017 UCLA study of breast cancer patients found tai chi as effective as conventional insomnia therapy (actually CBT)! So, what this new study suggests are different types of exercise, including even the very low impact options, or at least the ones you can do regularly, are all equally effective. I like tai chi, but I love all forms of exercise.

So when anyone asks me “Hey Dr. Moyad, which exercise is best?” then my response is always “The one YOU enjoy the most that YOU can stick with or adhere to for a long time.” Note the capital “YOU” in the previous sentence does not mean I am shouting, but rather emphasizing your importance when it comes to sleep (phew, I dodged that controversial column moment). Age and cancer treatments can compromise sleep, but what we are learning is regular simple movements allows the body in some cases to, once again, achieve deeper and more refreshing forms of sleep.

Radiotherapy’s Role in Metastatic Prostate Cancer Clarified

Men with 3 Bone Lesions and No Visceral Metastases See Clear Benefit

Adding radiation therapy (RT) to standard treatment improved failure-free survival (FFS) and overall survival (OS) for prostate cancer (PCa) patients with only a few bone metastases, an exploratory analysis of the multi-arm, multi-stage STAMPEDE trial found.

“Among the nearly 2,000 men in the study, adding RT to mostly androgen deprivaton therapy (ADT) improved both FFS (Hazard Ratio [HR] 0.57, 95% Confidence Interval [CI] 0.47-0.70) and OS (HR 0.62, 95% CI 0.46-0.83) in those with only non-regional lymph node metastasis or with fewer than 3 bone lesions and no visceral metastases,” reported Noel Clarke, MBBS, of the Christie NHS Foundation Trust in Manchester, England, and colleagues.

Men either with visceral metastasis or 4 or more bone lesions still had significantly improved FFS (HR 0.87, 95% CI 0.76-0.99, P=0.002 for interaction) with RT, but no overall survival benefit (HR 1.08, 95% CI 0.91-1.28, P=0.003 for interaction), according to the findings published online ahead of print in JAMA Oncology.

Primary findings from this part of STAMPEDE, showed that men with “low metastatic burden” had improved 3-year OS with the addition of RT to standard of care (SOC), 81 vs. 73%.

“The definition of low metastatic burden is not agreed upon internationally; it includes a range of definitions based on metastasis number (<3 to <10), various sites (bone, lymph node, and/or visceral metastasis), and different imaging modalities,” wrote Clarke and colleagues. “In our study, we built upon these prognostic criteria to evaluate systematically the predictive nature of metastatic burden based on conventional imaging using bone scan and computed tomography/magnetic resonance imaging.”

In an accompanying editorial, Bridget Koontz, MD, of Duke University School of Medicine in Durham, North Carolina, and Thomas Hope, MD, of the University of California San Francisco, said the findings help clarify which metastatic patients should be offered RT, but noted that a recent meta-analysis showed a survival benefit in men with fewer than 5 lesions.

“While the utility of prostate RT can be debated for a man with castration-sensitive PCa and 4 bone metastases, the overall take-home message is that local RT matters most in men with few metastases and good systemic control and that local RT should be applied more cautiously as the burden of disease increases,” they wrote.

Koontz and Hope added that number of metastases is a “rough surrogate” for disease volume on imaging, which has also been associated with PCa outcomes in this (Continued on page 5)
Radionuclide Treatment Wins in Third-Line Metastatic CRPC
Early Trial Shows Improved PFS, Response Rates Versus Cabazitaxel

Prostate-specific membrane antigen (PSMA)-targeted radionuclide therapy reduced the risk of disease progression or death versus cabazitaxel (Jevtana) in men with previously treated metastatic castration-resistant prostate cancer (mCRPC), and with fewer toxicities and better quality of life, a randomized phase II trial showed.

“In the so-called TheraP study, which involved 200 men with high PSA expression and progressive disease following docetaxel, lutetium-177 ($^{177}$Lu)PSMA-617 improved radiographic progression-free survival (PFS) over cabazitaxel (Hazard Ratio [HR] 0.63, 95% Confidence Interval [CI] 0.46-0.86, P=0.0028, a statistically significant difference),” reported Michael Hofman, MBBS, of the Peter MacCallum Cancer Centre in Melbourne, Australia.

While median radiographic PFS was identical, at 5.1 months in each arm, 12-month rates were 19% with the PSMA-targeted radionuclide therapy vs. 3% with cabazitaxel, according to findings presented at the virtual Genitourinary Cancers Symposium (GuCS) and published simultaneously in The Lancet. Overall survival (OS) data were not mature.

“Lutetium PSMA-617 represents a new class of effective therapy for men with CRPC,” said Hofman.

$L^1$$^7$Lu PSMA-617 is a small molecule that delivers high levels of beta-particle radiation (RT) to PSMA-expressing cells,” Hofman explained, “but low doses to normal tissue.

“A strength of the study is an active control arm using cabazitaxel – a validated life-prolonging therapy reinforced with the publication of the CARD trial,” he said.

Writing in an accompanying editorial, Thomas Hope, MD, of the University of California (UC) San Francisco, and Jerome Calais, MD, of the UC Los Angeles, agreed.

“Cabazitaxel is an effective therapy for men who have already received docetaxel,” they noted, while adding that other PSMA-targeted radiopharmaceutical therapy trials are using weaker comparator arms, which may limit their interpretation.

Hope and Calais called attention to the PFS curves in TheraP, which only separated at 6 months, by which point the PSMA-targeted agent outpaced cabazitaxel.

“This finding might be the most interesting aspect of this study and highlights two points. First, PSMA-targeted radiopharmaceutical therapy treatment is cumulative, unlike chemotherapy. Tumor cells receive doses of RT every 6 weeks, and therefore the treatment effect might not be shown immediately,” they wrote. “Second, a subpopulation of patients exist who have a prolonged benefit from PSMA-targeted radiopharmaceutical therapy, pushing out the tail of the PSMA-targeted radiopharmaceutical therapy progression-free survival curves.”

As previously reported, TheraP met its primary endpoint, with $^{177}$Lu PSMA-617 leading to a higher proportion of men with a 50% or greater reduction in PSA from baseline vs. cabazitaxel (66 vs. 37%; P <0.0001).

Objective response rates in the current study were doubled with the radiopharmaceutical therapy, at 49% compared with 24% with cabazitaxel. Men in the $^{177}$Lu PSMA-617 arm also had less pain following treatment, with 60% reporting improvements vs. 43% of those in the cabazitaxel arm (relative risk 1.4, 95% CI 0.9-2.2, P=0.10).

“Lutetium PSMA-617 was significantly more active than cabazitaxel with fewer grade (Continued on page 8)
A multichannel pipette tips filled with reaction mixture to amplify DNA in plastic wells

Scores with the 22-gene Decipher genomic classifier (GC) were independently associated with risk for metastasis, prostate cancer (PCa)-specific mortality (PCSM), and overall survival (OS) among men with recurrent PCa treated with salvage radiotherapy (RT) with or without bicalutamide.

“These results suggest that not all men with biochemically recurrent (BCR) disease after surgery will benefit from hormone therapy,” reported Felix Y. Feng, MD, of the University of California San Francisco, and colleagues online in JAMA Oncology. Using specimens from the phase III NRG/RTOG9601 clinical trial, Feng and colleagues generated GC scores from 352 men with median follow-up of 13 years. Patient GC scores were calculated on a continuous scale from 0 (lowest) to 1 (highest). Scores were then classified as low (42%), intermediate (38%), or high (20%) using previously established 0.45 and 0.60 GC score cutoffs. Multivariable analysis showed that the GC score as a continuous scale was independently associated with distant metastasis (HR 1.17; 95% CI 1.05-1.32; P=0.006, a statistically significant difference), PCSM (Hazard Ratio [HR] 1.39; 95% Confidence Interval [CI] 1.20-1.63; P<0.001), and OS (HR 1.17; 95% CI 1.06-1.29; P=0.0002) after adjustment for age, race/ethnicity, Gleason score, T stage, margin status, initial PSA level, and treatment arm. Similar results were seen when GC scores were analyzed by category. The analysis was supported by test-maker Decipher Biosciences.

In an accompanying editorial, Sean E. McGuire, MD, PhD, of the University of Texas MD Anderson Cancer Center in Houston, called the results “a hugely important milestone” as they represent “the first level-1 validation of the performance of the Decipher GC in a prospective, randomized, double-blind, phase III trial.” Although the study was not powered to detect an interaction by treatment arm with GC score, benefits for distant metastasis, PCSM, and OS observed with hormone therapy did appear to differ. One example the researchers noted was that the 12-year improvement in OS with hormone therapy in GC low scores was 2.4 vs. 8.9% with GC intermediate or high scores, which “may help guide shared decision-making,” they wrote. McGuire also noted that “this association was even stronger in men who were receiving early salvage RT.” GC score was also prognostic among men with PSA less than the median entry value of 0.7 ng/dL treated earlier with salvage RT. For distant metastasis the benefit of additional hormone therapy was estimated to be 0.4% for low GC compared with 11.2% for higher GC risk groups. For PCSM the values were 1.0 and 8.4%, and for OS, -7.8 and 4.6%, respectively. Although the confidence intervals for these crossed zero, the results “illustrate the potential utility of personalizing shared decision-making beyond using PSA to drive hormone therapy utilization,” the researchers wrote. In his editorial, McGuire said “the American Society of Clinical Oncology’s most recent guideline gave Decipher a score of intermediate for evidence of quality and moderate strength of recommendation for its use. Now, however, that may need revision.”

Indeed, Feng noted that Decipher GC is already clinically available and covered by many insurance carriers. “Thus, our findings can be relatively quickly incorporated into clinical practice,” Feng told MedPage Today. “For men with PCa recurrences post-surgery, I believe that the Decipher test can be helpful to guide decisions regarding who should receive RT alone or RT combined with hormone therapy.”

“At the end of the day,” Feng said, “the goal is to personalize not only hormone therapy, but all therapies for men with PCa. This study represents a good first step towards that goal.”

MedPage Today
11 February 2021

Radiotherapy’s Role in Metastatic Prostate Cancer Clarified (Continued from page 3)

dataset.

“This approach has advantages compared with counting lesions owing to the high interreader variability in bone scan interpretation,” they wrote. “We do not know if it is the number of metastases or the volume of metastatic disease that matters, or if both are equally important.”

The distinction, argued Koontz and Hope, will be of greater importance in the highly-sensitive prostate-specific membrane antigen (PSMA) PET era, when many more bone lesions are likely to be detected on imaging. STAMPEDE randomized 2,061 men (median age 68) to SOC with or without RT (55 Gy in 20 daily fractions over 4 weeks, or 36 Gy in 6 weekly fractions over 6 weeks). SOC predominantly involved ADT, but the trial was amended to allow docetaxel (about 20% received it). The current analysis included 1,939 men with evaluable imaging using conventional bone scans. In all, 82% had any bone metastases (plus or minus non-regional lymph nodes), 9% had only non-regional lymph node metastasis, and 9% had visceral or other sites of metastasis. Among the 577 men with 3 or more lesions, RT improved 3-year OS from 75 to 85% (HR 0.64, 95% CI 0.46-0.89) and FFS improved from 33 to 53% (HR 0.56, 95% CI 0.45-0.71). In the 1,010 patients with 4 or more lesions, OS was unchanged (53% without vs. 52% with RT), nor was it improved among the 171 men with visceral or other metastasis (56 vs. 53%, respectively). In the 181 patients with only non-regional lymph node metastasis, FFS at 3 years significantly improved from 29 to 51% with RT (HR 0.63, 95% CI 0.42-0.94), while OS showed a trend toward favoring RT (HR 0.60, 95% CI 0.33-1.09).

Limitations cited by the authors included the retrospective nature of the study and the fact that RT’s role has not been established with docetaxel or newer classes of agents in this setting.

MedPage Today
18 February 2021
ed androgen receptors and elevated intratumoral androgens, the overall patient population is heterogeneous in terms of androgen receptor resistance and sensitivity,” Rathkopf noted.

“Apalutamide disrupts androgen receptor signaling, whereas abiraterone inhibits androgen biosynthesis. Simultaneous inhibition of both pathways might provide additional clinical benefit beyond either drug’s individual activity,” she continued. The randomized phase III ACIS trial tested the hypothesis that 2 androgen-targeted drugs would be better than 1 against untreated mCRPC.

Investigators in 17 countries randomized 982 men to abiraterone and prednisone with or without apalutamide. The primary endpoint was investigator-assessed radiographic PFS, and OS was a key secondary endpoint.

The trial met the primary endpoint in March 2018 but follow-up continued until OS analysis was completed. Primary analysis showed a statistically significant 31% lower risk of disease progression or death with combined therapy (95% Confidence Interval [CI] 0.58-0.83).

While the difference in PFS increased from < 6 to 7.4 months, median OS did not differ significantly between the 2 treatment groups (HR 0.95, 95% CI 0.81-1.11). Prespecified secondary and exploratory endpoints, including initiation of chemotherapy, opioid use, pain, clinical progression, first subsequent anticancer therapy, and second PFS were similar.

More men treated with both drugs had at least a 50% decline in PSA level (79.5 vs. 72.9%, P=0.015) and undetectable PSA levels at some point during treatment. However, median time to PSA progression did not differ between the groups (13.8 vs. 12.0 months, P=0.076).

Subgroup analysis showed that PFS in men with visceral metastases was better with the combination (HR 0.69, 95% CI 0.45-1.05) as was OS (HR 0.76, 95% CI 0.52-1.10), and in men aged ≥75 (HR 0.54, 95% CI 0.40-0.73 and HR 0.75, 95% CI 0.59-0.96, respectively). Consistent with prior study data, men with PAM50 luminal subtype and average or high androgen receptor activity had numerically better PFS.

“No new or unexpected adverse events [AEs] occurred during the trial. The combination led to more fatigue, hypotension, skin rash, and cardiac disorders. Patient-reported outcomes declined over time in both groups, indicative of disease progression, but did not differ significantly,” Rathkopf reported.

“The trial could not determine whether escalation of androgen receptor signaling inhibition improves outcomes and whether continued androgen inhibition after progression is helpful,” said invited discussant Joshi J. Alumkal, MD, of the University of Michigan Rogel Cancer Center. “Results from prior studies addressing these questions were inconsistent. Biomarker investigation will play a key role in providing answers.

“Understanding the key drivers of these tumors may provide a roadmap for how to address the most aggressive subsets of CRPC tumors, who appear to do quite poorly, even with ARSI [androgen receptor signaling inhibition] escalation,” he said.

Presented at the 2021 GUcs, Abstract 9

MedPage Today
11 February 2021

CCR Score

(Continued from page 1)

termediate- or high-risk PCa derived minimal benefit from multimodality therapies, but the study carried certain limitations, included that RT dose and duration of ADT were not accounted for. Also, different types of RT techniques were used and a relatively small number of radiation subsets were studied.

The current validation study addressed these issues in 741 evaluable men with biopsy-proven intermediate (70%) or high-risk (30%) PCa based on NCCN criteria.

Tward and colleagues obtained biopsy tissue and performed genetic testing retrospectively, years after men were treated, eliminating risk of bias in treatment decisions. Median follow-up was 5.9 years. The validation study showed CCR score to be a better prognosticator of metastasis at 10 years compared with CAPRA or CCP scores alone:

- CCR: HR 2.21 (95% CI 1.70-2.87, C-index 0.78)
- CAPRA: HR 1.39 (95% CI 1.22-1.58, C-index 0.71)
- CCP: HR 2.04 (95% CI 1.48-2.79, C-index 0.69)

And CCR score was more accurate compared to the NCCN risk subgroups (C-index 0.72). In all NCCN subgroups (favorable, unfavorable intermediate, high/very high), the risk of metastasis at 10 years was below 5% when patients had a CCR score below the cutoff.

“Adding ADT to RT adds unnecessary morbidity for an extremely small absolute risk reduction in metastasis-free survival for many in the unfavorable intermediate-risk and a significant minority of high-risk men,” Tward said.

GUcs discussant Richard Valicenti, MD, of UC Davis School of Medicine, cautioned that no biomarker has been prospectively tested and shown to improve long-term outcomes in men with higher-risk PCa. “Clearly, the CCR score may provide highly precise personalized estimates and justifies testing in tiered and appropriately powered non-inferiority studies, according to NCCN risk groups,” he said. “Such studies could establish a highly individualized de-intensified approach to treating PCs conditioned on a below-the-multimodality-threshold strategy.”

Men were included if they received dose-escalated external beam RT (275.6 Gy at 1.8 Gy per fraction) with modern techniques and CT-based treatment plans. Those receiving pelvic nodal RT were allowed. Use and duration of ADT must have been captured.

About half of men had been treated with ADT plus RT. In men with unfavorable intermediate-risk cancer, ADT duration was considered “sufficient” if they received at least 4 months of ADT, and at least 18 months for men with high-risk cancer—matching current NCCN guideline recommendations. Less than half (44%) received some, but not sufficient, ADT per this criteria.

Presented at the 2021 GUcs, Abstract 195

MedPage Today
12 February 2021

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
er biomarkers such as PSA density to select, among the patients with positive MRI findings, those who need targeted biopsy (and those who may safely avoid it), and among men with negative MRI findings who may still deserve systematic biopsy,” he writes.

The Canadian PRECISE study was designed as a noninferiority trial in coordination with the European PRECISE study, but the Canadian version had several more features: It added risk-based eligibility, systematic follow-up of all men for 2 years, a repeat MRI in all untreated patients, investigation of fluid- and tissue-based biomarkers in the cohort, and an economic analysis.

PRECISE was conducted in 5 Canadian academic health sciences centers from 2017-2019. A total of 453 biopsy-naive men with a clinical suspicion of PCA were referred for prostate biopsy, of which 421 were evaluable per protocol. Clinical suspicion was defined as a ≥5% chance of grade group 2 or greater PCA. Men were also required to have serum PSA levels of 20 ng/mL or less and no concomitant indication to MRI.

Men randomly assigned to MRI underwent an MRI-targeted biopsy only if a lesion with a Prostate Imaging Reporting and Data System (PI-RADS) score of 3 or greater was identified, whereas all men in the other arm of the trial underwent a systematic TRUS-guided 12-core biopsy. The MRI approach identified more clinically significant cancers. Grade 2 or higher tumors were found in 79 (35%) of 227 men allocated to MRI-TB, vs. 67 (30%) of 225 men who underwent TRUS biopsy. MRI also reduced the need for a biopsy, allowing many men to avoid the associated pain, discomfort, and infection risks. Of 221 men who were randomly assigned to the MRI group, 83 (37%) had a negative MRI result and avoided biopsy. In contrast, all men in the TRUS group had a biopsy.

In addition, MRI was associated with a marked reduction in the diagnosis of clinically insignificant Interna-tional Society of Urological Pathology (ISUP) grade group 1 cancers (10% with MRI-TB vs. 22% with TRUS). Detection of such early cancers, under conventional protocols, often leads to unnecessary therapies or invasive procedures with significant side effects.

These results led the researchers to conclude that the strategy of MRI followed by MRI-guided biopsy only in men at risk of PCA “offers substantial advantages over an initial systematic biopsy.” The MRI strategy “results in similar detection rates of clinically significant PCs while avoiding biopsy in more than one third of men and reducing the diagnosis of clinically insignificant cancer,” the investigators point out.

Investigators acknowledged differences in both positive (Continued on page 8)

Combining Treatment Disappoints in Metastatic Castration-Resistant Prostate Cancer

Combining the tyrosine kinase inhibitor saracatinib with docetaxel does not benefit men with metastatic, castration-resistant prostate cancer (mCRPC), according to researchers. In a phase 1/2 study, the combination increased toxicity without improving progression-free or overall survival (PFS, OS, respectively).

Although we could safely combine the Src kinase inhibitor saracatinib with docetaxel, it did not show any improvement in outcomes when compared with docetaxel plus placebo. We therefore do not recommend proceeding to a phase 3 trial,” said investigator Robert J. Jones, MD, PhD, of the Institute of Cancer Sciences at the University of Glasgow, Scotland.

Jones presented the phase 1/2 trial results at the 2021 Genitourinary Cancers Symposium (Abstract 107). He explained that saracatinib targets Src family members, and Src activity is increased during the acquisition of castration resistance and during taxane resistance. Jones and colleagues therefore theorized that saracatinib could be beneficial for men with mCRPC.

The team tested their theory with the phase 1/2 trial, enrolling patients with mCRPC who had not previously received taxanes or radionucleotides. Jones reported results for 10 men in the phase 1 portion of the trial and 140 men in the phase 2 portion. In phase 1, patients received saracatinib at 50 mg, 125 mg, or 175 mg daily plus docetaxel at 75 mg/m². There were no dose-limiting toxicities or pharmacokinetic interactions in these patients, so the phase 2 dose of saracatinib (175 mg daily) was initiated. In phase 2, men were randomized to receive saracatinib plus docetaxel or placebo plus docetaxel.

Results: Safety and Efficacy

“In terms of efficacy, the trial failed to meet its primary endpoint of demonstrating an improvement in PFS. Indeed, there was a trend toward an improvement in PFS for patients receiving placebo,” Jones said. “Similarly, in this key secondary endpoint of OS, there was no benefit from the addition of saracatinib. And again, there was a trend toward an improved survival in patients receiving placebo.”

The median progression-free survival was 19 weeks with saracatinib and 29 weeks with placebo (adjusted hazard ratio [HR], 1.348). The median overall survival was 62 weeks with saracatinib and 83 weeks with placebo (adjusted HR, 1.422). Furthermore, there were no significant differences between the treatment arms for 2 other efficacy endpoints — maximum absolute change in PSA levels and absolute change in circulating tumor cell (CTC) count from baseline to cycle 3.

However, grade 3 or higher adverse events were more common in the saracatinib arm than in the placebo arm — 59% (41/69) and 41% (29/71), respectively. The most common grade 3 or higher adverse events (in the saracatinib and placebo arms, respectively) were neutropenia (25 vs. 8%), diarrhea (12 vs. 4%), and fatigue (6 vs. 4%).

This research was funded by the UK National Health Service and Cancer Research UK. Jones disclosed relationships with Astellas Pharma, AstraZeneca, Bayer, Bristol-Myers Squibb, and a number of other companies.

Medscape Medical News
12 February 2021

Check out the Us TOO Advanced Prostate Cancer Brochure at:
www.ustoo.org/AdvancedBrochure
Radionuclide Treatment in Third-Line Metastatic CRPC (Continued from page 4)

3/4 adverse events, and patient-reported outcomes in multiple domains favored lutetium PSMA."

Grade 3/4 toxicities occurred in 33% of men treated with \(^{77}\)Lu PSMA-617 vs. 53% with cabazitaxel, the most common being neutropenia (4 vs. 13%, respectively), thrombocytopenia (11 vs. 0%), anemia (8% each), diarrhea (1 vs. 5%), and fatigue (5 vs. 4%).

On the European Organization for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30), significant improvements with \(^{77}\)Lu PSMA-617 were seen in social functioning, fatigue, insomnia, and diarrhea, and all other measures trended in favor of the radionuclide group. There was also lower incidence of skin rash, sore hands/feet, altered taste, dizziness, urinary symptoms, and diarrhea with \(^{77}\)Lu PSMA-617.

The study also demonstrated improved deterioration-free survival (DFS) with \(^{77}\)Lu PSMA-617, which was defined as time to \(\geq10\) point deterioration in EORTC QLQ-C30 global health status, disease progression, death, or treatment discontinuation. At 6 months, DFS rates were 29% in the study arm vs. 13% in the cabazitaxel arm. At 12 months, these rates were 21 vs. 1%, respectively.

TheraP was an open-label, investigator-initiated phase II trial that from 2018 to 2019 randomized 200 men with metastatic CRPC who had previously been treated with docetaxel 1:1 to either \(^{77}\)Lu PSMA-617 (delivered intravenously every 6 weeks for up to 6 cycles, starting at 8.5 GBq and decreasing 0.5 GBq each cycle) or cabazitaxel (20 mg/m² via intravenously for up to 10 cycles).

“‘A paired diagnostic test involving PET-CT imaging with gallium-68 (\(^{68}\)Ga)-PSMA-11 was used to exclude men who might not benefit from the treatment. Men needed to have a PSMA SUVmax \(>20\) at any site for inclusion, as well as no FDG-positive or PSMA-negative sites of disease. After screening 291 men, 91 were excluded due to low PSMA expression (n=29), FDG-discordant disease (n=51), or other reasons (n=11). Fifteen patients dropped out in the cabazitaxel arm vs. none in the study arm, a limitation of the study,” Hofman noted.

Patients had a median age of 72 years, 91% had previously received androgen receptor-directed therapy (abiraterone, enzalutamide or both), and about 95% of patients had an ECOG performance status score of 0 or 1. PSA PFS showed a similar hazard ratio to the radiographic PFS analysis, like per-protocol sensitivity analyses. Presented at the 2021 GuCS, Abstract 6

MedPage Today
11 February 2021
Between the Sheets...  

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, PhD, APRN, CUCNS, Director of Sexual Health at NorthShore University HealthSystem and at Jesse Brown VA Medical Center in Chicago, IL. Dr. Albaugh is a board-certified advanced practice urology clinical nurse specialist, certified sexuality counselor and trained relationship counselor. He has completed Level 1 and 2 training from the Gottman Institute and has also trained with Andrew Christensen, PhD in Integrative Behavioral Couples Therapy. 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.

**QUESTION FROM PROSTATE CANCER SURVIVOR:**  
Do you have any advice to improve communication with my wife? Sometimes it feels like we are just on completely different pages when we are trying to talk to each other, especially if we disagree.

**RESPONSE FROM DR. JEFFREY ALBAUGH:**  
Thank you for your question and it is an important one to most couples. One of the number one issues identified by couples in relationship therapy is poor communication. It is important to approach communication with your partner from an open, receptive place. Keep in mind that you are on the same team as your partner. Your partner is not your adversary. The goal is not to be right, but rather to better understand each other and deepen the connection between you. You don’t have to agree, but you can respect and understand each other’s equally valid viewpoints. Remember you love this person.

When you want to communicate about something really important, you need to think about and carefully determine the best way to discuss it with your partner. You may want to process your own feelings prior to communicating with your partner. Think about an appropriate time to have the conversation. It is helpful to use “I” language rather than “you” language. No one wants to be criticized. Begin from a place of describing how you feel in light of a particular circumstance and also what you need from your partner. You must be specific and don’t generalize using expletives (for example you may say, “I felt hurt when you pulled your phone out during our date night last night as we were talking and I need us both to put our phones aside when we are having quality time together” instead of “You always pull out your phone when we are talking and I really hate when you do that”). You may want to soften up your delivery and make sure you are coming from a place of love and not a place of anger.

How you listen is incredibly important. Remember you have one mouth and two ears, so you should be listening more than you are speaking. If you want to understand your partner’s perspective and feelings as desperately as you want them to understand your perspective, you are ready to really listen and hear them. Listen carefully to your partner and don’t interrupt them. After they finish, try and paraphrase and acknowledge back to them what you heard them say. Restating what you heard your partner say is a way of making sure you received the message while acknowledging the value of what your partner said to you (for example: “I understand that you felt hurt when I pulled out my phone during the conversation last evening and you need us to put our phones aside when we are talking”). Focusing on understanding, listening and restating rather than creating your defense as your partner is speaking puts the focus on the information from your partner rather than on you and on being right.

If one or both of you is feeling flooded, triggered or overwhelmed, it is okay to take a break from the conversation, but it is very important to plan a time that you will come back to the conversation after you have had time to step back and process the argument. Unresolved issues can cause resentment, frustration and hurt feelings. It is important to avoid criticism, contempt (being disrespectful with a personal attack), defensiveness and stone walling (the silent treatment) according to world renowned couple therapist and researchers John and Julie Gottman ([https://www.gottman.com/blog/the-four-horsemen-recognizing-criticism-contempt-defensiveness-and-stonewalling](https://www.gottman.com/blog/the-four-horsemen-recognizing-criticism-contempt-defensiveness-and-stonewalling)). There are some great resources out there to help you have a better relationship and communicate better. You can find some helpful resources at [https://www.gottman.com/couples](https://www.gottman.com/couples) and also at [https://www.psychalive.org/communication-between-couples](https://www.psychalive.org/communication-between-couples). Good communication is a critical component of a good relationship and can lead to deeper more meaningful intimacy.

You can access the new edition of my book at [www.drieffalbaugh.com](http://www.drieffalbaugh.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](https://www.youtube.com/watch?v=Hiq0dDEb1l0&t=4483s).

**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:  
Us TOO International  
Between the Sheets  
2720 S. River Road, Suite 112  
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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).

27th Annual PCF Scientific Retreat – Top New Discoveries for Patients
PCF held its 27th Annual Scientific Retreat in late 2020 – virtually, of course. With no constraints of time or geography, there were a record 2,300+ registered attendees from 36 countries. Scientific Retreat is an opportunity for PCF-funded investigators and other experts in the field of prostate cancer research to learn from each other through presentations, discussions, and informal networking (in Zoom breakout rooms this year).

From 36 total panels and presentations, PCF’s Global Director of Research and Scientific Communications, Dr. Andrea Miyahira, has curated the Top New Discoveries for Patients. Stay tuned for more next month!

Testing a New Treatment for Metastatic CRPC
Presentation by Matthew Rettig, MD, of UCLA and the VA Greater Los Angeles Healthcare System

There is a crucial need for effective treatments for metastatic castration-resistant prostate cancer (mCRPC). One option involves immunotherapy, using the body’s natural T cells to recognize, bind to, and kill cancer cells. Bispecific T-cell engagers (BiTEs) are specially-designed antibody-based chimeric proteins that can bind to T-cells and tumor cells simultaneously. (Yes, “chimeric” is the technical term. Imagine the chimera monster from Greek mythology, composed of a lion, a goat, and a snake – but much, much smaller). When these treatments are infused into the patient, they find their way to the tumor, bringing the T cells with them.

An early phase trial by Dr. Matthew Rettig and team has found sustained positive responses in patients with mCRPC, with some patients even continuing to undergo treatment for more than 6 months. Large reductions in PSA were seen in the majority of cases, all of whom were previously not responding to multiple types of therapy. Overall, the treatment had a manageable safety profile as a single therapy. This trial is continuing to accrue patients, and is also beginning to test the efficacy and safety of this treatment in combination with the checkpoint immunotherapy pembrolizumab. Through initial testing, BiTEs have been shown to be a potentially viable option for mCRPC patients, illuminating another path toward disease control.

Biopsies Without a Needle
Presentation by Gerhardt Attard, MD, PhD, of University College London Cancer Institute

No one wants a prostate biopsy, but it’s currently the gold standard for prostate cancer diagnosis. For men with metastatic disease, if a biopsy is needed to look at changes in the cancer at distant sites in the body, it can be especially challenging. A “liquid biopsy” that would allow doctors to look at prostate cancer markers in blood has been the “holy grail” for years. Today, there are FDA-approved tests using circulating tumor DNA (ctDNA) as a liquid biopsy: DNA that has been released by tumor cells into the circulation and can be collected from patients by blood draws. Researchers are studying how change in the genetic material in ctDNA can be used as a biomarker to measure disease burden and predict patient outcomes.

PCF researchers expert on ctDNA have discovered a way to greatly improve on this method of liquid biopsies. Dr. Gerhardt Attard and his team are analyzing a modification of ctDNA known as a methylation pattern – rather than focusing on the DNA itself - which is better at indicating tumor burden than ctDNA levels alone. Their results suggest that this approach is superior in a number of ways and may be at the next “bleeding edge” of liquid biopsy science. While this technology is still in development, in the future, ctDNA methylation may be used to better classify prostate cancer for precision care.

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