Best of the 2013 AUA Annual Meeting

Highlights From the 2013 American Urological Association Meeting, May 4-8, 2013, San Diego, CA

[Rev Urol. *2013;15(2):72-81 doi: 10.3909/riu2013AUA]*

KEY WORDS

Transrectal ultrasound • Prostate biopsy • Nephrolithiasis • Shock wave lithotripsy • Overactive bladder • Interstitial cystitis • Chronic pelvic pain syndrome • Cystectomy • Erectile dysfunction • Prostate markers • PSA screening • Prostate cancer • *PCA3*

Over 2000 posters, abstracts, and videos were presented at the annual meeting of the American Urological Association (AUA), held this year in San Diego, CA, May 4-8, 2013. The editors of *Reviews in Urology* have culled an enormous volume of information from this premier source and present those findings that are the most relevant to the practicing urologist.

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Prostate Biopsy Complications

The complications of prostate biopsy were a major focus at the 2013 AUA meeting. In particular, there has been tremendous recent concern about an increasing frequency of infectious complications after prostate biopsy,[1] as reflected by their consideration in recent prostate cancer screening guidelines.[2]

Among 927 Canadian patients undergoing transrectal ultrasound (TRUS)-guided prostate biopsy in 2012, Rudzinski and Kawakami[3] reported that 4.4% of patients were admitted to the emergency room with infections. Sepsis occurred in 2.3% of cases, and the majority of infectious complications were caused by fluoroquinolone-resistant organisms. A small study by Sheehan and colleagues[4] showed that approximately one-third of patients had high levels of endotoxin in the serum following prostate biopsy. Although none of the patients in this study developed clinical infectious complications,

they expressed concern about the potential risks for susceptible individuals. By contrast, a higher rate of infectious complications (6.59%) was reported by Wei and associates[5] among 12,968 TRUS-guided prostate biopsies performed in Taiwan. In addition, 1.14% experienced massive bleeding and 9.76% had voiding difficulty. Urinary and infectious complications were significantly associated with increasing age and Charlson comorbidity index.

In a prospective study of 196 patients including 159 with complete follow-up, Murray and colleagues[6] reported transient decreases in erectile function (as measured by the International Index of Erectile Function) at 1 and 4 weeks after biopsy, but no significant difference from baseline by 3 months. Similarly, men undergoing prostate biopsy reported worse urinary symptoms (as measured by the International Prostate Symptom Score) at 1 week but this returned to baseline by the 4-week assessment.

Other studies evaluated patient-specific and contextual factors that could help predict the likelihood of prostate biopsy-related complications. Holland and colleagues[7] showed that men who had received $>$ 1 week of empiric ciprofloxacin for prostatitis within 8 weeks of prostate biopsy were significantly more likely to have infectious complications (odds ratio [OR] 3.93; 95% confidence interval [CI], 1.36-11.31; $P = .01$). Gade and associates[8] reported that prostate volume, catheterization, and Asian ethnicity were significantly associated with the risk of infection after prostate biopsy. The authors suggested that patients be screened carefully prior to biopsy for these and other previously identified risk factors (eg, foreign travel, recent hospital exposure). In this study, undergoing prostate biopsy for the indication of active surveillance was not associated with the frequency of infectious complications. Meanwhile, Ehdaie and coworkers[9] reported that in an active surveillance population, the number of previous biopsies was significantly associated with the risk of infection (OR 1.34; 95% CI, 1.02-1.76; $P = .036$). Another issue concerning active surveillance is the possible risk of erectile dysfunction (ED) from repeated surveillance biopsies, as was previously suggested by Fujita and coworkers.[10] However, an abstract by Albaugh and colleagues[11] of men on active surveillance found that the number of repeat biopsies and total cores taken were not associated with sexual dysfunction.

With regard to prostate biopsy prophylaxis, most centers worldwide have traditionally prescribed fluoroquinolones.[12] However, increases in resistance have led to investigation into alternate and targeted strategies as a way to decrease infection risk. For example, Mitchell and associates[13] noted an increasing frequency of infectious complications after prostate biopsy at a Veterans Affairs Medical Center. Based on the local antibiogram, the prophylaxis regimen was changed from 3 days of oral fluoroquinolones to a single intramuscular dose of gentamicin (240 mg) and ceftriaxone (1 g) 1 hour prior to biopsy. The frequency of hospitalization for infectious complications decreased significantly following this change ($P = .002$). The authors emphasized the importance of antimicrobial stewardship and recommended giving "locally targeted" prophylaxis based on the institutional antibiogram, because there are geographic differences in resistant patterns.

Another way to give targeted prophylaxis is at the individual level using rectal swab cultures to assess for fluoroquinolone-resistant bacteria and selectively treat those patients with an alternate agent.[14] A logistical consideration is whether rectal swab cultures from an earlier clinic visit would reflect the flora present at the time of subsequent biopsy. Liss and associates[15] addressed this issue by performing serial rectal swab cultures in a small population of veterans. They showed that rectal swab cultures performed at the initial office visit had a 77.8% positive predictive value and 95.9% negative predictive value for fluoroquinolone-resistant bacteria at the time of biopsy. Additional prospective studies are warranted to clarify which of these strategies is most cost effective to improve the safety of prostate biopsy moving forward.

[Stacy Loeb, MD]

Kidney Stones

There has been a paucity of recent research on the mechanisms of struvite kidney stone formation. Krambeck and colleagues[16] characterized the papillary morphology in patients found to have struvite stones during percutaneous nephrostolithotomy. Digital endoscopy and papillary biopsies were performed; 25% of patients were found to have ductal plugging on endoscopy—a significantly larger proportion than what was encountered in those with idiopathic calcium oxalate (CaOx) stones, as well as in control subjects. The extent of papillary plaque quantified with endoscopy was similar to controls and less prominent than the CaOx group. Another 15% of the cohort was found to have ductal plugging on histologic evaluation. These results suggest that events within the papillary ducts may play a role in the pathogenesis of struvite stones in humans.

The 2012 AUA Clinical Effectiveness Protocols for Imaging

in the Management of Ureteral Calculous Disease recommended the performance of renal ultrasonography after ureteroscopic stone removal to screen for ureteral stricture, an uncommon but significant occurrence. Some patients who develop this problem are asymptomatic. Sutherland and colleagues[17] performed a one- and two-way analysis to determine the economic implications of screening all patients versus only those who had symptoms suggesting ureteral obstruction. They found that universal screening carried a $130 per patient higher cost than the selective approach. Thus, the price to potentially save a renal unit is relatively low. In addition, it may lower the physician's "legal bother"!

Kidney stone formation is linked to various aspects of lifestyle. A number of studies presented at this meeting support these associations. Diet is an important component of lifestyle. Sorensen and associates[18] analyzed the Women's Health Initiative (WHI) cohort—84,225 postmenopausal women—and found in a multivariate analysis that greater intake of fruits, vegetables, and fiber (all healthy food choices) reduced the risk of kidney stone formation. Similar associations in Japan were reported at the AUA Annual Meeting. Yasui and colleagues[19] found that the incidence of nephrolithiasis was lower in regions of Japan where the intake of fruit was higher and the consumption of sugar and eggs was lower. De and Monga[20] used the stone prevalence data from the National Health and Nutrition Examination Survey, spanning 1974 to 2010, and the US Department of Agriculture data on food distribution during the same time period to generate linear models. Stone prevalence significantly increased over this time course. They found strong positive correlations between total daily calories, fat, and protein consumption and stone prevalence. Better tools are needed to assess the longitudinal impact of diet on stone disease. Bell and associates[21] developed a novel food frequency questionnaire for assessing nutritional risk factors for stone formation consisting of 33 items. A pilot study was done using healthy adults. The average time for completing the questionnaire was 5 minutes. The food frequency questionnaire was compared with a nutrient analysis of dietary recall by a registered dietician. There were excellent correlations for fluid, fruit, and vegetables. Further adjustments in this instrument will need to be made before a validation study is undertaken. Physical activity is another important aspect of lifestyle. Sorensen and colleagues[22] performed another analysis of the WHI cohort and found that greater physical activity reduced stone risk in postmenopausal women. Although the total amount of physical activity had a significant impact, exercise intensity did not. They also reported that increased caloric consumption positively correlated with stone risk in this population.

Stone fragments in the lower pole have difficulty passing into the central portion of the renal collecting system and down the ureter after shock wave lithotripsy (SWL). A novel focused ultrasound device has been developed that propels stone fragments to different areas in the renal collecting system. Connors and associates[23] assessed this in a porcine model in which stones and nickel beads were displaced out of calyces to the renal pelvis or ureter. Careful histologic analysis demonstrated no renal injury. The investigators are trying to obtain US Food and Drug Administration approval for performing a feasibility study in humans.

Patients who are candidates for stone-removing procedures should be counseled regarding the potential for successful stone elimination. Lantz and associates[24] have developed a nomogram for predicting success with SWL of renal and ureteral stones. The key components are stone surface area, stone location, stone attenuation, and skin-to-stone distance. Kadlec and colleagues[25] used a nonlinear regression model to predict a stone-free status with a single session of SWL, percutaneous nephrostolithotomy, and ureteroscopic stone removal. Input variables included the type of procedure, body mass index (BMI), and several stone-based parameters including those used in the aforementioned model. Okhunov and coworkers[26] have developed a nephrolithometry scoring system (stone size [S], tract length [T], obstruction [O], number of involved calices [N], and essence or stone density [E]: S.T.O.N.E.) to predict results with percutaneous nephrolithotomy (PCNL). They reported that this system has interobserver reliability. Akhavein and colleagues[27] demonstrated that the S.T.O.N.E. system was reproducible and predictive of treatment success with PCNL. Smith and associates[28] (Clinical Research Office of the Endourological Society) developed another nephrolithometry instrument for predicting success with PCNL using their large multicentered database. The components of this system included surgeon volume, prior treatment, BMI, stone burden, stone location, number of stones, presence of staghorn stone, and existence of renal anomalies. They reported that this system was predictive of stone-free status. All of these profiled systems will need to be further assessed and validated with prospective trials.

These studies are reflective of the progress that is being made in defining the pathophysiology of stone formation, development of novel technology, and tools for predicting treatment success. These accomplishments should contribute greatly to the care of patients with nephrolithiasis.

[Dean Assimos, MD]

Overactive Bladder and Interstitial Cystitis

In the area of interstitial cystitis/bladder pain syndrome (IC/BPS), a new gene target was presented at this year's AUA meeting. Molecular evidence of the novel *HCN2* gene as a new diagnostic and treatment tool for IC/BPS was presented.[29] It is estimated that between 3 and 8 million women in America are affected by IC/BPS. *HCN2* carries a hyperpolarization inward current that is important for driving the repetitive firing of pain fibers, which makes them a promising drug target. Recent research has shown that mice that had the *HCN2* gene deleted had decreased neuropathic pain.

Pain symptoms of IC/BPS patients may be initiated by *HCN2*-driven action potential firing in pain-sensitive nerve endings. Quantitative real-time polymerase chain reaction (qPCR) was carried out in normal and IC/BPS bladder urothelium and detrusor tissue. qPCR analysis of isolated complementary DNA from human urothelium tissue revealed definite expression of *HCN2*. Genomic DNA contamination in RNA samples was ruled out using control subjects without the addition of reverse transcriptase complementary DNA synthesis. This study identified a fourfold increase in *HCN2* expression in the urothelium of patients with IC/BPS.

In summary, this is a surprising new discovery of a novel gene that is critical for chronic pain and lays the groundwork for the development of new drugs to treat chronic pain by blocking *HCN2*. In addition, the discovery can lead to a new understanding for the underlying mechanism of IC/BPS disease and lead to the potential discovery of new methods to treat IC/BPS without altering normal urination.

[Michael B. Chancellor, MD]

Evolving Therapeutic Approaches for Urologic/Chronic Pelvic Pain Syndromes

The annual meeting of the AUA provides a forum each year for researchers to describe new modalities of therapy for urologic chronic pelvic pain syndromes (CPPS) such as IC/BPS and chronic prostatitis (CP)/CPPS. Some of these treatments may ultimately not be clinically effective, whereas others become part of the urologists' armamentarium to manage these difficult urologic conditions. The presentations of new and novel therapeutic approaches for our patients with these conditions are perhaps some of the most exciting aspects of the IC and prostatitis AUA podium and poster sessions.

IC/BPS

Previous studies presented at the AUA suggest that neuromodulation from an InterStim (Medtronic, Minneapolis, MN) implant at the spinal cord level may not only provide benefit in terms of urinary urgency and frequency but also possibly pain. Chancellor and associates[30] showed that patients with IC/BPS who responded favorably to neuromodulation showed a corresponding decrease in urine levels of chemokines. These results support a hypothesis for the action of chemokines as downstream effectors of neuromodulation response in the bladder, and may provide noninvasive treatment predictors.

Pinto and coworkers[31] investigated the benefits of onabotulinum toxin A injections in ulcerative and nonulcerative forms of IC/BPS. They observed that both groups (albeit small numbers: 10 ulcerative and 10 nonulcerative IC/BPS patients) responded equally to trigonal onabotulinum toxin A with a marked decrease in pain, frequency, and nocturia, with the benefits lasting 9 to 10 months.

Tripp and colleagues[32] examined the comprehensive list of pain appraisal and behavioral coping strategies as mechanisms in the relationship between pain and quality of life (QoL) in patients with IC/BPS. In 190 patients recruited from tertiary care urology clinics, investigators' data suggested that catastrophic appraisals and illness-focused behavioral coping act as mechanisms driving the negative associations between pain and subsequent QoL. The catastrophizing mediation effect supports the hypothesis that symptoms may become mentally disabling through the cognitive mechanisms. These investigators' results further support the expanding science emphasizing the importance of biopsychosocial therapeutic models in association with our traditional medical and surgical approaches.

Cystectomy is generally considered a last resort option in the treatment of intractable IC/BPS. Norus and colleagues[33] evaluated the possibility of creating a urinary diversion without cystectomy. They reported their outcomes over the past 10 years of urinary diversion for IC/BPS with or without cystectomy. Their conclusions, based on 20 patients who underwent ileal conduit without cystectomy, was that this approach may be an appropriate option in performing urinary diversion in IC/BPS patients and

was not associated with recurrent or intractable urinary tract infections or, for most patients, intractable pelvic pain. It seems reasonable to consider delayed cystectomy due to persistent symptoms and, in fact, two of their patients underwent a subsequent cystectomy.

The traditional monotherapy, stepwise therapy algorithm for the treatment of IC/BPS fails a great number of patients. Nickel and colleagues[34] evaluated a flexible therapeutic strategy for IC/BPS using an individualized phenotype-directed treatment plan based on a clinically based UPOINT (Urinary, Psychosocial, Organ-specific, Infection, Neuropathic/non-bladder, Tenderness of pelvic floor) categorization, which has been advocated for CP/CPPS in men. Patients referred to a specialized tertiary IC/BPS clinic for consultation were categorized according to their UPOINT status and were treated according to best evidence-based phenotype-directed treatment plans. Almost 50% of previously treated patients referred to a tertiary IC/BPS clinic, regardless of complexity or severity of condition, experienced clinically significant improvement using this type of individualized phenotype-directed therapeutic approach. Investigators also noticed a disconnect between symptom questionnaire improvement and patients' sense of well-being, QoL, and activity level. Therefore, it may be more important to direct the goal of therapy toward improved QoL and increase in life activities rather than simply amelioration of severity of symptoms.

CP/CPPS

More clinicians are becoming disillusioned with the traditional monotherapy, stepwise approach to the treatment of CP/CPPS and previous studies presented at the AUA suggested that various approaches to multimodal therapy, either standardized approaches or phenotypically directed approaches, appear to be superior. Giannontoni and associates[35] evaluated a multimodal therapy approach that included an antidepressant, an α-blocker, and saw palmetto extract. In a small, randomized trial of 38 patients, they noted that the multimodal therapeutic approach is statistically and clinically significantly better in controlling clinical symptoms and improving psychologic status and QoL in patients affected by CP/CPPS.

Many investigators and clinicians have speculated that phosphodiesterase type 5 (PDE5) inhibitors may have an effect on CP/CPPS. Kogan and colleagues[36] compared 10 patients with CPPS and 30 age-matched volunteers and noted that a decreased blood supply of the prostate correlated with symptoms of this condition. Follow-up histologic findings were consistent with ischemic changes likely due to vascular disease in CP/CPPS; the authors concluded that chronic ischemia of the prostate may be a factor in the development of CPPS. Park and associates[37] went on to further investigate the efficacy of mirodenafil, a selective PDE5 inhibitor, in middle-aged patients with CP/CPPS. In this study, which randomized 88 men with CPPS who received either levofloxacin or levofloxacin and mirodenafil, the investigators showed significant symptomatic improvement in the mirodenafil-treated group in terms of prostatitis symptom score and sexual functioning. Lieser and Shoskes[38] confirmed that a high proportion of men with CP/CPPS also complain of ED. They also showed that a small but potentially significant group of these patients had abnormal hemodynamics, further supporting an etiologic link between ED and CP/CPPS, with a potential treatment modality in the form of PDE5 inhibitor therapy. This approach should be further investigated.

In a similar study, Tripp and coworkers[39] evaluated 168 men enrolled in a CP cohort study from North American tertiary care centers. These studies suggested that illness-focused coping, helpless catastrophic pain appraisals, and friends (social support) act as mechanisms that drive and buffer the negative association between pain and QoL. Urologists managing this condition, for which we have no cure, will have to address the behavioral, cognitive, and environmental mechanisms that are involved in perpetuating the pain and poor QoL in this patient population.

[J. Curtis Nickel, MD]

Prostate Markers

Once again, markers in prostate cancer were a major theme at the 2013 annual meeting of the AUA. The impact of the US Preventive Task Force recommendation on prostate-specific antigen (PSA) screening was the subject of several papers. Undoubtedly, the revised AUA guidelines reported at this meeting will generate even more reports. The new AUA guidelines do not recommend screening in men aged 40 to 54 years who are at average risk. The panel stated that, for men aged 55 to 69 years, shared decision-making should be utilized for those considering PSA screening based on each individual's values and preferences. The panel does not recommend routine PSA screening in men > age 70 years or in those with < a 10- to 15-year life expectancy.

Cohn and associates[40] reported on the effect of the task force recommendations on the frequency

of PSA testing by primary care physicians. They studied men aged 40 to 79 years with no history of prostate cancer or urologic referral. The proportion of men with at least one PSA test over a 5-month period before and after the Task Force recommendations was evaluated. A total of 41,171 men were evaluated (18,399 before and 22,772 after screening); the prescreening group was significantly younger and less likely to be insured by Blue Shield ($P < .001$ for both). After the Task Force recommendation, there was a significant decrease in overall screening (7.9% vs 6.9%; $P < .001$). This was most common in men aged 70 to 79 years in whom the decrease was 9.1% versus 5.6%, white men (9.2% vs 7.7%), and men with a prior PSA < 2.5 (10.5% vs 8.5%); all were significant at $P < .001$. The authors concluded that, in the short time since the recommendation announcement, there has already been a significant change in practice of primary care providers.

Yamaguchi and coworkers[41] described the use of initial PSA testing in men without a diagnosis of prostate cancer at the Cleveland Clinic (Cleveland, OH) between 1999 and 2012. A total of 228,233 patients were identified; mean age was 60.2 years. A significant number of men were tested who fell outside of the recommended age (1.8% among those aged 35 to 40 years and 4.2% in men aged 80 to 85 years). The number of PSA tests per patient year increased to 1.4 for those aged > 85 years. The authors concluded that there were significant deviations from institutional PSA guidelines with respect to age at initiation of screening, frequency, and life expectancy at initial testing. The impact of the Task Force recommendations in a large health system was described by Aslani and colleagues.[42] All screening PSAs performed at university hospitals in northeastern Ohio between January 2008 and August 2012 were evaluated. In all, 42,211 PSA determinations were performed; 47.5% were from internal medicine practitioners, 28.8% from family practitioners, and 9.2% from urologists. There was an increase over time until May 2012 (final US Preventive Services Task Force report), and then a subsequent significant decrease. The greatest decrease was in urban teaching hospitals, the primary care setting, and in patients aged 50 to 59 years and aged 70 to 79 years.

In an attempt to predict the effect of a reversal to the pre–PSA era in patients presenting with prostate cancer, Adams and colleagues[43] examined patients presenting to a county hospital with a PSA > 100 ng/mL. The hospital, which serves a large underinsured population, examined the records of those presenting between 1988 and 2008. A total of 71 men were identified (14.4% of all prostate cancers diagnosed during this period). No man had been screened at this institution previously. The median PSA level was 399 ng/mL. Median survival was 18 months with 9.6% of men surviving > 3 years. Presenting PSA, Gleason score, ethnicity, and presence of metastases did not affect survival. Nadir posttherapy PSA < 1.0 and age < 60 years were associated with better survival. The authors commented on the importance of screening and improved access.

The use of the Prostate Health Index (PHI) for identifying clinically significant prostate cancer was investigated by Sanda and coworkers.[44] In all, 658 men were investigated; all had a PSA of 4 to 10 ng/mL and were aged ≥ 50 years with clinical stage T1c. PHI was compared with taps, free PSA (fPSA), and free to total PSA antigen ratio (%fPSA). At 90% sensitivity, PHI specificity was 31.1% versus 19.8% and 10.8% for % fPSA and PSA, respectively ($P < .001$). The PHI level correlated with the aggressiveness of the cancer. Using a cutoff of 27 for PHI clinically significant cancer was rare (8% Epstein criteria, 2.9% Gleason 3+4, and 0.7% Gleason 4+3). At 90% sensitivity, 18.8% of men with a negative biopsy result or insignificant cancer could have avoided the biopsy.

PCA3 has gained increased utilization primarily to identify men who have had a negative prostate biopsy result but may harbor malignancy. Ahn and colleagues[45] investigated variation in *PCA3* by comparing men who had two or more determinations. A total of 78 men who had at least one repeat *PCA3* test within 1 year were investigated. The mean absolute difference was 17.4 (range 0.2-104.7). Overall, 22% of men had both a positive and negative test using 35 as the cutoff. The authors note that this significant variation in test result may suggest repeat confirmatory testing and advocate for prospective evaluation.

High-grade prostatic intraepithelial neoplasia (PIN) continues to generate investigation. Kingman and colleagues[46] reported on 614 men with high-grade PIN among 6101 prostate biopsies. With a median follow-up of 38.6 months, among 64% of men with repeat biopsy, cancer was detected in 140 (22.8%). The majority (82%) had a primary Gleason score of ≤ 3. Gleason score of ≥ 7 was observed in 39%. The authors state that as the incidence of cancer was similar to that reported in a repeat biopsy series based on PSA elevation, high-grade PIN is not a significant predictor of cancer and should not be an independent indication for repeat biopsy.

Miyoshi and colleagues[47] measured testosterone levels in prostate

tissue obtained during needle biopsy in an effort to resolve the issue of androgen level and prostate cancer malignant potential. In all, 196 men underwent peripheral zone biopsy in addition to systematic biopsies; testosterone and dihydroxytestosterone (DHT) were measured using liquid chromatography–mass spectrometry. Median testosterone and DHT in blood were 3551 and 331 pg/mL, respectively, and in tissue 0.57 and 7.06 pg/mL, respectively. In multivariate analysis, both serum PSA and tissue testosterone levels correlated with poor prognosis, including high Gleason score ($P = .041$), advanced clinical stage ($P = .002$), and high proportion of positive biopsies ($P = .001$).

The Decipher (GenomeDx Biosciences, Vancouver, British Columbia, Canada) is a genomic test in development for determining risk for progression after radical prostatectomy (RP). Karnes and associates[48] used this genomic classifier in men with high-risk prostate cancer in a case cohort design. A total of 219 men were investigated; 72% had a low test result and the incidence of metastases at 5 and 10 years was 3% and 6%, respectively. For the 28% of men with a high test result, the incidence of metastases was 17% and 25%. The co-occurrence index for the Decipher test was 0.79, significantly better than any single clinical variable, and this remained the only variable that was significant in multivariate analysis.

Cooperberg and coworkers[49] reported on the 17-gene assay developed at the Cleveland Clinic and validated at the University of California-San Francisco. The study evaluated the assay's ability to predict pathologic stage and grade among 395 men undergoing RP who were considered candidates for active surveillance. The assay predicted high grade ($\geq$ Gleason 4+3) and pT3 or greater disease ($P < .005$) after adjusting for standard clinicopathologic parameters, including Cancer of the Prostate Risk Assessment (CAPRA) score.

Freedland and associates[50] reported on the use of a 46-gene cell cycle progression (CCP) signature to predict outcome in men undergoing primary external beam radiation therapy for clinically localized prostate cancer. A total of 141 men were evaluated and more than half were black. The Phoenix definition for biochemical recurrence (BCR) was utilized (nadir + 2 ng/mL); 13% had BCR. CCP was a significant predictor of BCR on univariate analysis (hazard ratio [HR] for one unit of CCP score 2.55; $P = .0017$) and was the only predictor that was significant in multivariate analysis (HR 2.09; $P = .035$). There was no evidence for interaction between CCP and clinicopathologic variables or ethnicity.

Schlomm and colleagues[51] reported on the value of the 46-gene CCP signature to predict outcome from RP; 249 men were investigated. The test result was a highly significant predictor of BCR ($P = .000031$) and remained significant after adjustment of Gleason score and PSA (HR 1.6 per unit of CCP score; $P = .0068$). The assay differentiated pT2 from pT3 (HR 1.8; $P = .00027$).

[Michael K. Brawer, MD]

Dr. Brawer is an employee of Myriad Genetics Laboratories (Salt Lake City, UT), the provider of Prolaris testing.

Prostate Cancer

Many excellent presentations on localized prostate cancer were made at this year's annual meeting of the AUA, with an emphasis on patient selection or stratification criteria for before, during, or after treatment. Several of these particularly thought-provoking presentations piqued our interest.

Daskivich and colleagues[52] aimed to address overtreatment of prostate cancer by exploring the risk of other-cause, nonprostate cancer mortality endured by a cohort of men with early-stage disease. A group of 3183 men with early-stage prostate cancer was identified from the Prostate Cancer Outcomes Study cohort and was assessed for the presence of 12 comorbid conditions at diagnosis: diabetes, stroke, myocardial infarction, ulcer, congestive heart failure, angina, liver disease, arthritis, hypertension, depression, inflammatory bowel disease, and chronic lung disease. The risk of other-cause mortality was then defined as a function of comorbidity count and age at baseline (age 55 vs 65 vs 75 years). They also analyzed cancer-specific mortality based on aggressive versus conservative prostate cancer management across comorbidity groups. As the comorbidity count rose, so did the cumulative other-cause mortality, up to a 57% other-cause mortality rate at 14 years after diagnosis among men with $\geq$ three comorbidities. For men with $\geq$ three comorbidities, the HR for 10-year other-cause mortality doubled with each increasing decade of age past 55 years. Most importantly, men with $\geq$ two comorbidities did not suffer an increase in cancer-specific mortality when treated conservatively during a 10-year follow-up period. Any older man with multiple major comorbidities should take stock in these findings before electing to undergo aggressive intervention for low-risk prostate cancer.

A poster presented by Ellimoottil and colleagues[53] compared outcomes between open versus robotic prostatectomy among obese patients. A contemporary group of prostatectomy patients from the 2010 Nationwide Inpatient Sample were identified who had a diagnosis

of obesity or morbid obesity, and blood transfusion rates, length of stay (LOS), total hospital charges, and perioperative complications were recorded. In all, 6.6% of men undergoing RP were diagnosed with obesity. Interestingly, in 2010, the rates of robotic, open, and laparoscopic prostatectomy were similar between obese and nonobese men. Obese men undergoing open RP had significantly higher blood transfusion rates compared with robotic RP (9.9% vs 2.9%) and higher LOS (2.8 days vs 2.0 days). Conversely, hospital charges were higher with robotic RP ($31,636 open vs $45,638 robotic). A trend toward lower perioperative complication rates among obese men undergoing robotic RP was detected before controlling for age, comorbidity, and other factors. These data suggest that a robotic approach may decrease perioperative adverse events among obese men, although this effect is tempered by the high degree of comorbidity existing within this demographic at baseline. Urologists in the United States do not yet seem to have adopted the practice of stratifying their patients to surgical approach based on the presence of morbid obesity.

Another thought-provoking poster was presented by Preston and colleagues,[54] in which the authors ascertained the risk of developing high-grade prostate cancer among men taking the 5-α reductase inhibitor, finasteride. The US-based Health Professionals Follow-up Study was queried from between 1996 and 2010 and 38,430 men aged 40 to 75 years were identified who were free of prostate cancer at baseline. Finasteride use was assessed every 2 years, and multivariate analysis, including other putative risk exposures for prostate cancer, was performed. In all, 3710 men (9.7%) developed prostate cancer during follow-up, of which 578 (15.6%) were advanced and 463 (12.5%) were high-grade; 2920 (7.6%) of men reported using finasteride. After adjusting for confounding risk factors, having ever used finasteride was significantly associated with lower risk for total disease (relative risk [RR] 0.77), Gleason 7 disease (RR 0.66), and low-grade disease (RR 0.73). Surprisingly, finasteride use was not associated with risk of high-grade or lethal disease. Although the authors did not look specifically at 5-α reductase use for prostate cancer chemoprevention, this result nevertheless stands in contradistinction to prior reports and suggests that there is still more to this story than we know.

Richie and colleagues[55] presented phase II clinical data on the use of the antiandrogen abiraterone acetate (AA) for neoadjuvant treatment of localized high-risk prostate cancer. They compared a neoadjuvant combination of AA with the luteinizing hormone-releasing hormone (LHRH) agonist leuprolide acetate (LHRHa) against LHRHa alone. The primary endpoint was intraprostatic androgen level. High-risk men were defined as having 3 $\geq$ biopsies demonstrating at least Gleason $\geq$ 7 (4+3) prostate cancer, T3, PSA $>$ 10 ng/mL, or PSA velocity $>$ 2 ng/mL/year. In all, 58 men were randomized to either 12 weeks LHRHa alone followed by another 12 weeks of LHRHa and AA plus prednisone (28 men), or to 24 weeks of combination LHRH and AA plus prednisone (30 men). A prostate biopsy was performed to assay intraprostatic androgen levels in all men at 12 weeks, and RP was performed at 24 weeks. Men on combination neoadjuvant therapy were significantly more likely to achieve PSA nadir within 12 weeks than were control subjects (90% vs 4%), although, by 24 weeks, a similar number of men in both arms had achieved PSA nadir. The combined pathologic complete response rate was significantly higher for men in the combination neoadjuvant arm (34% vs 15%), and only the combination regimen was effective in significantly lowering serum dehydroepiandrosterone (DHEA) and DHEA sulfate levels, albeit to still-detectable levels. This provocative study suggests that combination neoadjuvant therapy with LHRH agonists and abiraterone are well tolerated and offer demonstrably enhanced pathologic complete response rates compared with LHRHa alone. We will be interested to see whether these findings translate into long-term oncologic results.

Moreira and associates[56] suggested that the clinical significance of finding inflammation in prostate biopsies counterintuitively portends a lower risk of subsequently developing prostate cancer. A total of 6269 men with PSA between 2.5 and 10 ng/mL and a prior negative biopsy result were analyzed from the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study population. All men had baseline and 2-year prostate biopsies, and multiple prostate inflammatory and prostate cancer risk factors were accounted for on multivariate analysis. Overall, prostate inflammation, either acute or chronic, was highly prevalent in the study population. Men who had acute inflammation on biopsy tended to be significantly younger, whereas men with chronic inflammation were significantly older. The REDUCE treatment arm assignment did not affect the incidence of inflammation. On univariate and multivariate analysis, both acute (OR 0.75) and chronic (OR 0.65) baseline inflammation were significantly associated with a lower risk of developing subsequent prostate

cancer at 2 years. This observation suggests one of two things: either a biologic link between prostate inflammation and lower prostate cancer risk, or conflation of an elevated PSA due to nonspecific inflammation with increased risk of positive biopsy. This may be of reassurance to men with elevated PSA and a finding of inflammation on an otherwise negative biopsy result.

Finally, Jeong and colleagues[57] used a novel approach to address the lack of tactile feedback inherent to contemporary robotic surgery. The authors employed their Modified Organ Retrieval for Intraoperative Examination (MORE) technique, in which the prostate is extracted ex vivo during robotic-assisted RP (RARP) through a specialized periumbilical 10-mm access port, allowing real-time handling of the prostate by the surgeon with his or her hands. A total of 117 patients with a $>$ 25% a priori risk of extraprostatic extension (EPE), as measured using the Partin tables, underwent MORE-RARP; areas suspicious for positive margin were sent for frozen section and, if necessary, additional resection was performed. A comparison of men with EPE (pT3a) on final pathology was made between control and experimental surgical groups. Men undergoing MORE-RARP had a significantly lower probability of positive margin (RR 2.6), and the site selected for frozen section biopsy matched the EPE site at final pathology 70.8% of the time with MORE-RARP. The authors demonstrate superior outcomes when a basic principle of open surgery—physical digital manipulation of the specimen—is extended to robotic surgery. This approach might bridge a gap between the open and robotic approach for patients who are good robotic candidates, insofar as tactile appreciation of prostate capsular integrity is concerned.

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