BPH Plus Prostate Cancer Therapy and Markers Featured at EAU

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At the recent European Association of Urology (EAU) Congress, over 3,000 urologists from around the world heard about exciting discoveries related to benign prostatic hyperplasia (BPH)/lower urinary tract symptoms (LUTS) and prostate cancer. In this brief update, we will highlight some of the findings and the clinical significance of a few of these important papers.

BPH/LUTS

For decades now, the patterns of growth of prostate tissue for men with LUTS and clinical BPH have been estimated from cross-sectional data or autopsy studies reported from men with either an unknown history of LUTS or lacking any symptoms of BPH. Roehrborn and colleagues[1] reported the patterns of growth for a clinically well characterized group of men followed in a longitudinal fashion for over 4 years. This group of over 3,000 men took part in the placebo arm of the controlled, randomized long-term PLESS (Proscar Long-term Efficacy and Safety Study) trial of finasteride (Proscar®). Prostate volumes, symptom scores, quality-of-life (QOL) measurements, and urinary flow rates were obtained at regular intervals for over 4 years. Prostate growth ranged from 1.7 to 3.1 mL in the first year and was dependent on the decade of life. An overall growth rate of 1.8 mL/year was noted. Prostatic growth rate was strongly PSA dependent. These findings support further investigation into the pathophysiology of prostatic growth among men with LUTS and may, with further elucidation, identify an age range in which men are at greatest risk for prostatic growth and/or development of LUTS and in which pharmacologic intervention may have its optimal influence.

Kella and associates[2] demonstrated that the waiting time prior to achieving an accurate flow rate recording in a busy urology clinic can be reduced by nearly 1 hour with a single oral dose of furosemide (Lasix®) 20 mg, without significantly affecting flow rate. The authors of this paper randomized in a crossover manner on 2 separate clinic visits 99 volunteers to receive an oral dose of 20 mg of furosemide prior to measurement of a urinary flow rate. After administration of the diuretic, the voided volume increased (269 no diuretic vs 318 with diuretic, $P<.01$), the flow rate was similar (19.9 mL/s vs 21.1 mL/s), and the time to void dramatically decreased (155 min no diuretic vs 80 min with diuretic, $P<.001$). This study reports an easy method for decreasing the time to void without affecting the results for urinary flow rates in a busy urology clinic. Caution should be taken to obtain a careful medical history and list of medications prior to administering oral diuretics to men for this purpose.

Prior to this important paper by Djavan and colleagues,[3] men in urinary retention requiring indwelling catheter drainage were discouraged from undergoing treatment with transurethral microwave therapy (TUMT). Most devices even list "urinary retention" as an absolute contraindication to treatment with microwave therapy. These authors enrolled 31 consecutive men with symptomatic BPH who were in urinary retention to be treated with TUMT (Targis®). They measured time with catheter after treatment, International Prostate Symptoms Scores (IPSS), urinary flow rates (Qmax), QOL scores, and pressure flow studies at 1, 2, 4, 6, and 12 weeks following treatment. By 1 week following treatment, 31% of the men had regained the ability to void spontaneously. At all time intervals, QOL, Qmax, and IPSS were improved for the group. Only 2/31 men failed to return to spontaneous voiding at 16 weeks and were classified as failures. This study demonstrates that urinary retention need not be a contraindication to treatment of patients with LUTS/BPH with TUMT.

In a study by Francisca and associates,[4] TUMT was administered to 57 consecutive men during an anesthesia-free single 30-minute treatment.

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Key words
Benign prostatic hyperplasia (BPH) • Transurethral microwave therapy • Lower urinary tract symptoms (LUTS) • Prostate specific antigen (PSA) • Kallikrein • Insulin-like growth factor • Therapy, microwave • Prostatectomy

Main Points

- Urinary retention need not be a contraindication to using transurethral microwave therapy for treatment of patients with LUTS/BPH.
- cPSA may provide similar specificity to %fPSA with the use of only 1 assay, but multicenter trials need to be done.
- The ratio of fPSA/PSA-α_2-macroglobulin may further improve specificity for prostate cancer diagnosis.
- For early detection of prostate cancer, an assay using the ratio of human kallikrein type 2 to fPSA is being investigated.
- A bridge catheter used as an adjuvant to transurethral microwave therapy may hasten the recovery period.

This protocol (TUMT 3.0, Prostatron) was designed to decrease the treatment time required for TUMT while simultaneously decreasing the discomfort experienced by the patient during treatment. Fifty-seven men (mean age, 66 years) with prostates averaging 63 g were treated with this experimental shortened treatment protocol (30 minutes vs 1 hour). The authors demonstrated a decrease in Qmax, IPSS, and QOL similar to that seen with the standard treatment protocol over a 6-month period. The average catheterization time was, however, reported to be 18 days. The men experienced no serious complications. This preliminary report of this shortened TUMT treatment protocol awaits validation in a randomized fashion, yet demonstrates promising results regarding the delivery of TUMT in a more efficient manner in the office setting.

Men treated with TUMT often experience profound yet transient LUTS and even urinary retention that may last up to 3 weeks following treatment. In addition, the maximal effects of TUMT are often not realized for 3 to 4 months following treatment. These authors investigated the safety, efficacy and feasibility of placement of a temporary bridge catheter after TUMT instead of the traditional indwelling catheter.[5] In this study, 54 men with symptomatic BPH/LUTS were treated with TUMT (Targis) using the standard protocol. After treatment, a prostatic bridge catheter (PBC) was placed and was left indwelling for 1 month. Qmax, IPSS, and QOL were determined at periodic intervals during and after PBC placement. The results were compared with a cohort of historic controls who received a standard indwelling catheter after treatment (typically for only 24 hours). Men receiving the PBC demonstrated improvement in Qmax, IPSS, and QOL scores faster and to a greater degree than the historic controls with the standard catheter. It was possible for 88.9% of the men to keep the PBC in place for the entire month. Early PBC catheter removal was required in 5.6% of the men for retention and/or catheter migration. These authors have demonstrated that the PBC can safely serve as an important early adjuvant to TUMT and hasten the recovery period and the perceived improvement in symptoms.

Prostate Cancer

There were many excellent papers pertaining to prostate cancer presented in Stockholm. Several papers regarding surgical technique and new/existing tumor markers deserve mention.

Two papers demonstrated a laparoscopic approach to radical prostatectomy. Abbou and colleagues[6] reported on retropubic removal of the prostate via a laparoscopic approach. Five men (mean age, 65.6 years), stage T1c (3), T2a (2), with preoperative PSA levels averaging 12.1 ng/mL and biopsy Gleason scores averaging 5.6 were chosen. Four laparoscopic trocars were utilized. The seminal vesicles were dissected first in a retrograde fashion. The prostate was then dissected from the anterior face of the rectum toward the apex. The dorsal vein and puboprostatic ligaments were approached from the anterior surface of the prostate. The bladder neck and lateral borders of the prostate were then dissected. The urethra was divided, the bladder neck reconstructed, and the vesicourethral anastomosis completed with 6 interrupted sutures. The specimen was removed via a sac through an enlarged umbilical trocar site. Surgical time averaged 419 minutes (6.9 hours), blood loss averaged 950 mL, and hospitalization averaged 7.8 days. One positive surgical margin was encountered, and the first patient (20%) developed a vesicourethral anastomosis leak that required prolonged catheterization. All men were continent at 1 month. Potency was not reported. This report demonstrated the feasibility of this approach to radical prostatectomy, yet prolonged operating room time, excessive blood loss, and double the length of stay compared with that seen with standard retropubic radical prostatectomy will continue to limit this approach. The second report detailed the laparoscopic approach for 38 men treated between 2/98 and 9/98.[7] The patients in this cohort were aged 65 years (mean), had a mean PSA of 10.0 ng/mL, T1c (20) and T2 (18), and a median Gleason score of 6. Open conversion was required in 13% of

the cases (4% of the later cases). Nineteen percent required blood transfusion. One rectal injury was noted and repaired laparoscopically without a long-term problem. The average operating time was 270 minutes (4.5 hours), and the mean hospital stay was 7 days. Only 12 men underwent lymphadenectomy, and all were N0. No positive surgical margins were reported. No data regarding potency were reported. Ten of 15 men with sufficient follow-up were reported to be continent. This report again demonstrates the feasibility of this approach by this group. Much more work, however, is required to justify the authors' report of this method being "perfectly and routinely feasible" for the rest of the world.

A study by the group from Toronto[8] evaluated intraoperative stimulation of the cavernous nerves during nerve-sparing radical prostatectomy. The authors reported 1-year follow-up on 25 men in whom cavernous nerve stimulation was utilized to guide nerve-sparing prostatectomy. They reported 89% tumescence response during stimulation at the time of surgery. Ninety-four percent of these men have documented potency postoperatively. The authors reported no adverse events associated with use of the device and only a 12% positive surgical margin rate. Large multicenter, randomized, controlled studies are in progress to further evaluate this technology.

Many new and interesting tumor markers were discussed during the 14th Congress of the EAU. Brawer and colleagues reported a multi-institutional study investigating the clinical utility of measuring cPSA (complexed-PSA, Bayer assay) as a single assay alternative to the standard use of 2 assays (total PSA [tPSA] and free PSA) used to determine percent free-PSA (%fPSA).[9] PSA circulates bound to a variety of endogenous protease inhibitors (α_1-antichymotrysin is the most abundant). This assay uses a negative subtraction or masking of all "free" unbound-PSA with cold unlabeled antibody to fPSA and accurately quantifies the proportion of PSA that is "complexed" or bound to other proteins. These authors demonstrated in a retrospective, archival sera cohort of over 250 men presenting for prostate biopsy that cPSA provides similar specificity (decrease in unnecessary biopsy) to that seen by %fPSA with the need for only 1 assay. The economic implications of these findings, while not expounded in this presentation, may be immense. These findings await validation in a prospective multicenter trial.

Zhang and associates[10] reported for the first time a new assay that measures the previously unmeasurable proportion of tPSA that is found engulfed by the endogenous protease inhibitor α_2-macroglobulin (A2M). The standard conventional tPSA assay does not estimate this fraction of PSA due to the inability of the antibodies to reach the PSA that is felt to be "caged" by the A2M like a small bird safe within a wire cage. This new assay is based on the removal of all other forms of immunoreative PSA in the circulation by immunoadsorption. The PSA-A2M is then denatured at high pH, and the resultant PSA, which is now "free of the cage," can be measured by a conventional PSA assay. They studied 73 men with prostate cancer and 53 with BPH with a tPSA range of 4 to 20 ng/mL. The proportion of PSA-A2M in the men with BPH (11%) was significantly higher than that in the men with prostate cancer (7%) ($P<.001$). The ratio of fPSA/PSA-A2M further improved cancer specificity. This new assay has the potential for improving our ability to diagnose prostate cancer. Cost issues, independent validation, and assay performance characteristics as well as a prospective study are still to be reported.

Both Cutting and associates[11] and Djavan and associates[12] reported on the use of serum insulin-like growth factor (IGF-1) for early detection of prostate cancer. The Djavan group reported a positive study in which the ratio of IGF-1 to tPSA improved the performance of tPSA for early detection. No comparison with %fPSA was reported. This prospective preliminary study of 158 men who underwent 2 sets of prostate biopsy highlights not only the possible clinical role of IGF-1 for early detection, but also helps us to better understand the relationship between PSA, IGF-1, and it's binding proteins. Further study is warranted. Cutting and colleagues reported a negative prospective study of 94 men who underwent biopsy of the prostate. In their study, 37 men had prostate cancer. They found no significant difference between the IGF-1 levels of those with cancer compared with those with no evidence of malignancy. Differences in the median age of the different groups may help explain this negative result, as IGF-1 levels are known to change with advancing age. These 2 studies signify the present state of understanding regarding IGF-1 for cancer detection. The jury is still out on this issue. Stay tuned.

Finally, human kallikrein 2 (hK2) is a new marker for prostate cancer that deserves mention. hK2 is a serine protease that is a "first cousin" to PSA with 80% sequence homology, similar androgen dependence, chromosome 19 localization, and high specificity to prostate tissue. Unlike PSA, hK2 increases its expression at both the mRNA and the protein level with increasing tumor grade and degree of aggressiveness. Boeken and colleagues[13] reported on the clinical utility of the ratio of hK2 to fPSA for early detection of prostate cancer. This new assay demonstrated relatively low cross-reactivity with PSA.

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Faculty
Included were:
Douglas A. Canning, MD, Director, Division of Urology and Assistant Professor, Pediatric Urology, Children's Hospital of Philadelphia
Paramjit S. Chandhoke, MD, Professor of Urology and Renal Medicine, University of Colorado
Steven A. Kaplan, MD, Professor and Vice Chairman, Department of Urology, Columbia Presbyterian Medical Center
Elspeth M. McDougall, MD, Associate Professor of Urologic Surgery, Washington University Medical School
Craig S. Niederberger, MD, Assistant Professor and Chief of Andrology, University of Illinois
Urs E. Studer, MD, Professor and Chairman, Department of Urology, University of Bern, Switzerland
Horst Zincke, MD, Professor of Urology, Mayo Medical School

Critique panel
Included were:
David A. Bloom, MD, Professor of Urology, University of Michigan
Ralph V. Clayman, MD, Professor of Surgery and Chief of Pediatric Urology, University of Michigan
Jay Y. Gillenwater, MD, Professor, Department of Urology, University of Virginia School of Medicine
Jack W. McAninch, MD, Professor of Urology, University of California at San Francisco School of Medicine
Randall B. Meacham, MD, Associate Professor of Surgery/Urology, University of Colorado Health Sciences Center
Michael K. Brawer, MD, Director, Northwest Prostate Institute

erally was well tolerated, there was significant associated morbidity (rectal injury in 6%; bladder neck contraction in 21%; and urinary incontinence in 51%, defined as wearing any pads). Obviously, there is a pressing need for new therapeutic strategies for these patients. □

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When coupled with fPSA (good kallikrein), hK2 (bad kallikrein) as the ratio hK2/fPSA, the reduction in the number of unnecessary biopsies without decreasing the detection of cancer was better than that seen by %fPSA alone. This assay has immediate clinical applicability and should see its way to our armamentarium soon. □

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