

UPDATE ON PROSTATE HEALTH

*A Focus on Benign Prostatic Hyperplasia
and Prostate Cancer Prevention*



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HIGHLIGHTS FROM THE 2006 AUA ANNUAL MEETING

TARGET AUDIENCE

This supplement is intended for urologists, urology residents, and other physicians treating prostate cancer.

STATEMENT OF NEED

Within the demographic context of an aging population, urologic health has assumed an increasingly prominent position in the overall health status of the American male. Prostate disease, in particular, is one of the most common health issues in men. Most men 50 years of age or older have prostate enlargement (benign prostatic hyperplasia [BPH] and/or lower urinary tract symptoms [LUTS]). The prevalence of both conditions increases substantially with each subsequent decade of life. Despite advances in treatment that have reduced mortality, prostate cancer remains the most common malignancy in men and the second leading cause of cancer death. Both the concepts and processes of managing prostate disease have evolved substantially in recent years. Growing recognition of the relationships among BPH, LUTS, and male sexual dysfunction has provided the impetus to explore new approaches to treat the conditions. The positive results of the Prostate Cancer Prevention Trial (PCPT) have provided the first hard evidence that the disease can be prevented.

LEARNING OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- Discuss the evidence linking BPH, LUTS, and sexual dysfunction
- Describe new and novel approaches to treatment of BPH and LUTS
- Recognize the therapeutic potential of minimally invasive treatment of BPH in the form of transurethral needle ablation
- Describe the potential benefits of prophylactic use of a 5-alpha-reductase inhibitor for prostate cancer prevention
- Explain the context of the “high-grade cancer controversy” associated with the PCPT

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LAST REVIEW DATE: August 15, 2006 **RELEASE DATE:** September 1, 2006

EXPIRATION DATE: September 30, 2007

This educational activity is jointly sponsored by Medical Education Resources, Inc, and cme², an independent subsidiary of Advanstar Communications Inc, publisher of *Urology Times*.



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Supported by an unrestricted educational grant from

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INTRODUCTION: EVOLVING CONCEPTS IN PROSTATE DISEASE

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Prostate disease, including prostate cancer and benign prostatic hyperplasia (BPH), remains one of the most common clinical problems confronting urologists and other physicians who provide care for men through the Veterans Affairs Health Care System.

A milestone in prostate cancer occurred in early 2006 when the American Cancer Society (ACS) released statistics showing the first-ever decrease in prostate cancer deaths. During 2006, an estimated 27,350 American men will die of prostate cancer, a decrease of 10% compared with 2005. However, prostate cancer continues to lead the way in terms of new cancer cases in men, as the ACS predicts that 234,460 American men will be diagnosed with the condition in 2006.¹

Lower urinary tract symptoms (LUTS) and prostate enlargement have become ubiquitous among aging men. An estimated 75% of men older than 50 years eventually develop BPH, LUTS, or both.² After age 85 years, almost all men have at least microscopic evidence of BPH.³

The following educational activity summarizes some of the newest data related to prostate cancer prevention and

BPH/LUTS, as reported at the 2006 American Urological Association (AUA) meeting. The summaries include new information pertinent to the controversy surrounding the Prostate Cancer Prevention Trial (PCPT). The PCPT showed a nearly 25% reduction in the risk of developing prostate cancer in men treated with finasteride for 7 years.⁴ However, significantly more men in the finasteride arm developed high-grade prostate cancer, a finding that has often overshadowed the primary result of the trial in the 3 years since the PCPT was reported.

Claus G. Roehrborn, MD, reviews the evidence supporting a role for 5-alpha-reductase inhibitors (5ARIs) in prostate cancer chemoprevention. He also reviews data from the PCPT and contrasts its design and objectives with those of an ongoing prevention trial with dutasteride.

Alberto Briganti, MD, and colleagues report data from a large patient series indicating that prostate volume influences the likelihood of detecting cancer (including high-grade cancer) during biopsy. According to the data, the odds of cancer detection increase as prostate volume decreases. The volume-reducing effect of 5ARIs on the prostate has been suggested as an explanation for the difference in high-grade cancer in the PCPT.

The Briganti study raises an issue that urologists should keep in mind when evaluating the PCPT data. In the PCPT, prostate volume did not differ between treatment groups at baseline, but a difference was seen after several years of treatment with finasteride. That represents a very different clinical situation compared with a review of untreated men whose prostates inherently vary in size.

Continuing the examination of prostate volume and cancer detection, Robert J. Serfling, PhD, and coworkers presented data from a mathematical evaluation of prostate volume and cancer detection. They concluded that shrinkage of the prostate by finasteride would increase the rate of prostate cancer detection. Their model also suggested biopsy parameters for different-sized prostates.

Eric A. Klein, MD, discussed data implicating a virus in the origin of at least some cases of prostate cancer. Though very early in the examination process, the findings to date are intriguing and suggest the potential for new approaches to treatment and possibly prevention of prostate cancer.

Within the realm of BPH/LUTS, Steve A. Kaplan, MD, reflected on the growing awareness of the overlap among overactive bladder (OAB), prostate symptoms, and sexual dysfunction in men. The evidence presented to date indicates that muscarinic receptor antagonists have a role in the treatment of OAB in men as well as women. New studies reported at the AUA meeting showed that phosphodiesterase type 5 inhibitors might improve urinary symptoms as well as sexual dysfunction. In addition, Kevin McVary, MD, FACS, reviewed clinical experience with transurethral needle ablation as a minimally invasive option for treatment of BPH/LUTS.

Collectively, these summaries provide insights into the evolving concepts related to prostate cancer chemoprevention and treatment of BPH.

REFERENCES

1. American Cancer Society. *Cancer Facts & Figures 2006*. Atlanta, Ga: American Cancer Society; 2006.
2. Da Silva FC. Benign prostatic hyperplasia: natural evolution versus medical treatment. *Eur Urol*. 1997;32(suppl 2):34-37.
3. McConnell JD, Barry MJ, Bruskewitz RC, et al. *Benign Prostatic Hyperplasia: Diagnosis and Treatment*. Clinical Practice Guideline, Number 8. Rockville, Md: Agency for Health Care Policy and Research, Public Health Service, US Department of Health and Human Services; 1994.
4. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med*. 2003;349:215-224.

■ THE ROLE OF 5-ALPHA-REDUCTASE INHIBITORS IN CHEMOPREVENTION OF PROSTATE CANCER

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An abundance of evidence implicates androgens in the development of prostate cancer. For example, a decade ago data from the Physicians' Health Study showed that men with higher testosterone levels had an increased risk for prostate cancer.¹

The association between androgens and prostate cancer provided the rationale to use 5-alpha-reductase inhibitors (5ARIs) for chemoprevention of prostate cancer. From laboratory investigations to large clinical trials, data have emerged to support the chemopreventive potential of 5ARIs. The evidence includes:

- Reduced proliferative activity in prostate cancer cells exposed to a 5ARI²
- Inhibition of tumor growth in rats³
- Delayed rise in prostate-specific antigen (PSA) following prostatectomy and reduced PSA levels in previously untreated men⁴
- Reduced incidence of prostate cancer in men treated prophylactically with a 5ARI⁵

The Prostate Cancer Prevention Trial (PCPT) provided the strongest evidence to date that chemoprevention with a 5ARI reduces prostate cancer risk.⁵ The PCPT involved 18,882 low-risk men ≥ 55 years of age, randomized to 7 years of treatment with finasteride or placebo. For-cause prostate biopsies were performed on the basis of PSA values or prostate examination, and all patients had end-of-study biopsies.

The primary result of the PCPT was a 24.8% reduction in prostate cancer risk in the finasteride group. A similar reduction in prostate cancer risk occurred across all major subsets analyzed. The PCPT also confirmed the beneficial effect of 5ARIs for reducing other prostate-related outcomes.

However, enthusiasm for the benefits observed in the PCPT was dampened by the observation that significantly more high-grade cancers (Gleason scores 7–10) occurred in the finasteride arm of the study. The finding gave rise to speculation that finasteride might induce high-grade cancer.

Since publication of the primary PCPT results, several lines of evidence have emerged to provide a strong argument that the disparity in high-grade cancer was an artifactual finding. Much of that work has yet to be published, but an example of the emerging data came from a study reported recently by Kulkarni and colleagues.⁶ A comparison of biopsy results and prostatectomy specimens obtained from men with prostate cancer showed that the likelihood of detecting high-grade cancer increased with smaller prostates. Finasteride is known to reduce prostate volume, and men in the finasteride group in the PCPT had smaller prostates compared with men in the placebo group.

Finasteride is a selective inhibitor of type 2 5AR. However, expression of type 1 5AR may play a relatively greater role in the development of prostate cancer. Comparison of 5AR gene expression in normal prostates, men with benign prostatic hyperplasia (BPH), and prostate cancer shows that type 1 5AR mRNA levels are greater in prostate cancer than in BPH or normal prostates. In contrast, type 2 5AR mRNA levels are decreased in primary prostate cancer compared with normal and BPH tissues.⁷

Dutasteride inhibits both type 1 and type 2 5AR. The impact of dual inhibition on prostate cancer risk is unknown but currently under investigation. However, pooled data from

placebo-controlled studies of dutasteride in BPH showed that patients treated with dutasteride had a significantly lower incidence of prostate cancer.⁸

The chemopreventive potential of dutasteride is being evaluated in the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial.⁹ REDUCE involves at-risk men—those who need a prostate biopsy as a result of findings from a clinical evaluation. This group of patients would likely be targeted by an approach to population-based screening for prostate cancer.

Every man enrolled in REDUCE will have a prostate biopsy at entry, followed by randomization to treatment with dutasteride or placebo for 4 years. Follow-up biopsies will be performed at 2 and 4 years, and for-cause biopsies may occur at any time during the 4 years of treatment and follow-up. Results of the trial are still several years away.

In summary, 5ARIs provide a promising new option for chemoprevention of prostate cancer. The increase in higher-grade tumors in the finasteride groups is associated with prostate volume reduction. Results from the REDUCE trial will help clarify the role of dual inhibition of 5AR in the chemoprevention of prostate cancer.

REFERENCES

1. Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. *J Natl Cancer Inst.* 1996;88:1118-1126.
2. Bologna M, Muzi P, Biondi L, Festuccia C, Vincenzini C. Finasteride dose-dependently reduces the proliferation rate of the LnCap human prostatic cancer cell line in vitro. *Urology.* 1995;45:282-290.
3. Lamb JC, Levy MA, Johnson RK, Isaacs JT. Response of rate and human prostatic cancers to the novel 5 alpha-reductase inhibitor, SK&F 105657. *Prostate.* 1992;21:15-34.
4. Andriole G, Lieber M, Smith J, et al. Treatment with finasteride following radical prostatectomy for prostate cancer. *Urology.* 1995;45:491-497.
5. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med.* 2003;349:215-224.
6. Kulkarni GS, Al-Azab R, Lockwood G, et al. Evidence for a biopsy derived grade artifact among larger prostate glands. *J Urol.* 2006;175:505-509.
7. Thomas LN, Lazier CB, Gupta R, et al. Differential alterations in 5alpha-reductase type 1 and type 2 levels during development and progression of prostate cancer. *Prostate.* 2005;63:231-239.
8. Andriole GL, Roehrborn C, Schulman C, Slawin KM, Somerville M, Rittmaster RS. Effect of dutasteride on the detection of prostate cancer in men with benign prostatic hyperplasia. *Urology.* 2004;64:537-541.
9. Gomella LG. Chemoprevention using dutasteride: the REDUCE trial. *Curr Opin Urol.* 2005;15:29-32.

■ STUDY CONFIRMS ASSOCIATION BETWEEN PROSTATE VOLUME AND HIGH-GRADE CANCER

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The Prostate Cancer Prevention Trial (PCPT) showed that treatment with the 5-alpha-reductase inhibitor finasteride for 7 years reduced the risk of prostate cancer by 24.8% compared with placebo in men who had no clinical indications of cancer at baseline.¹ However, the trial results created controversy with the finding of a higher rate of high-grade (Gleason grades 7–10) prostate cancer in the finasteride arm.

Because treatment with finasteride reduced prostate volume by nearly 25% compared with placebo, an alternative means of expressing the high-grade cancer findings would be to say that men with larger prostates had lower rates of high-grade cancer than men who underwent sextant biopsy. We hypothesized that tumors detected in large prostates are associated with more favorable characteristics.

Univariate and multivariate logistic regression models were used to examine the association between prostate volume and high-grade prostate cancer, extracapsular extension, and seminal vesicle invasion in radical prostatectomy specimens. Other variables entered into the model include patient age, prostate-specific antigen (PSA) value, clinical stage, and year of surgery.

For the analysis, we used data from 3412 consecutive patients aged 39 to 78.6 years who underwent radical prostatectomy at 2 large European centers. The patients had a median PSA value of 6.7 ng/mL (range of 0.12-50 ng/mL) and a median prostate volume of 44 cc (range of 11-224 cc). Clinical stage was T1c in 66.6% of cases, T2 in 32.4% of cases, and T3 in 1% of cases. Biopsy Gleason scores were 6 in 68.9% of cases, 7 in 28% of cases, and 8 to 10 in 3.1% of cases.

High-grade prostate cancer was found in 1806 (52.5%) of the radical prostatectomy specimens. In univariate analysis, high-grade prostate cancer had a statistically significant inverse association with prostate volume. When prostate volumes were separated into quartiles (<34 cc, 34-44 cc, 45-58 cc, and ≥59 cc) the proportion of prostatectomy specimens containing high-grade cancer decreased from 56.7% and 56.8% in the first 2 quartiles to 53.2% in the third quartile and 42.3% in the fourth quartile. Patient age, pretreatment PSA, clinical stage, year of surgery, and prostate volume also were significant predictors of high-grade prostate cancer at radical prostatectomy ($P<.005$). All predictors except for year of surgery retained their statistical significance in multivariate analysis ($P<.001$).

Our data demonstrate that increasing gland size is associated with more favorable pathological features at radical prostatectomy. The findings support the observation in the PCPT of a lower rate of high-grade cancers in larger prostates. Thus, our results seem to show that in the PCPT trial, the increased rate of high-grade prostate cancer in small glands might have been gland-volume-related.

REFERENCE

1. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med.* 2003;349:215-224.

■ MODEL PREDICTS INCREASED CANCER DETECTION RATE IN SMALLER PROSTATES

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Previous studies have demonstrated a negative correlation between total prostate volume and prostate cancer detection on biopsy. By decreasing total prostate volume, 5-alpha-reductase inhibitors (5ARIs) could enhance cancer detection by reducing the benign component of the gland, thus increasing the likelihood of detecting cancer in a biopsy core.

In the Prostate Cancer Prevention Trial (PCPT), treatment with finasteride for 7 years reduced the risk of prostate cancer by 24.8% compared with placebo. However, high-grade tumors (Gleason grades 7-10) occurred significantly more often in the finasteride group.¹ Investigators hypothesized that a detection bias related to reduced prostate volume accounted for the difference in high-grade tumors between treatment groups.

We constructed a mathematical model to predict the likelihood of a positive biopsy. The model derives from the input variables of tumor volume (derived from prostate-specific antigen [PSA] values), peripheral-zone (PZ) and transition-zone (TZ) volumes,

and number of biopsy cores. We used the model to examine whether the reduction in prostate volume observed with finasteride in the PCPT might alter detection of tumors.

A key output of the model is the number of PZ and TZ biopsy cores needed to detect with 90% probability a specific tumor configuration of 4 nodules based on 2 ranges of PSA values (4-10 ng/mL and >10 ng/mL) that were translated into tumor volumes. We considered a range of tumor nodule volumes of approximately 0.03-1.5 cc, corresponding to tumor volumes of approximately 0.5-3.0 cc. Probabilities were estimated for the likelihood of different nodule distributions in the TZ and PZ.

To study the effects of the prostate volume reduction that occurred in the finasteride arm of the PCPT, we entered prostate volumes of 20-80 cc in 10-cc increments into the model, as well as a prostate volume reduction of 25%. Tumor volumes entered into the model ranged between 0.5 and 3.0 cc. Additionally, the model included 4 biopsy patterns that matched the protocols used in the PCPT and in the ongoing Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial: standard sextant biopsy; 10 cores, with 6 in the PZ and 4 in the TZ; 10 cores, with 8 in the PZ and 2 in the TZ; and 10 cores, all in the PZ.

Application of the model to different tumor volumes showed that the number of biopsy cores required to detect cancer with at least 90% probability increases as prostate volume rises and as tumor volume decreases. For example, to detect a 1-cc tumor in a 20-cc prostate would require 6 biopsy cores, but to detect the same 1-cc tumor in an 80-cc prostate would require 22 biopsy cores.

We examined the impact of a 25% decrease in prostate cancer volume, as occurred with finasteride in the PCPT, on detection of tumors with sextant biopsy across the volume range of 0.5 to 3.0 cc. The results showed that the probability of detecting a 0.5-cc tumor in a 20-cc prostate would increase by 17%, decreasing to 0% improvement for detection of a 3-cc tumor (in the latter case, the detection probability is already at 1 and cannot be improved). A similar pattern emerged for larger prostates. A 25% reduction in prostate volume would have a relatively greater impact on detection of smaller tumors compared with larger tumors.

Applying the model to detection of a 1-cc tumor in the REDUCE patient population (which has a mean prostate volume of 46 cc) resulted in an increased detection rate of 11% to 17% for 10 biopsy cores, assuming no effect of dutasteride on tumor volume.

This model provides guidance on the optimal number of biopsy cores for men with different prostate volumes and tumor sizes. The computations suggest that sextant biopsy suffices only for a 20-cc or smaller prostate for men who have a tumor volume of 1 cc, and for a 40-cc or smaller prostate in the case of a 3-cc tumor. Similarly, a 12-core biopsy suffices for a prostate size of 40 cc or smaller for men with a 1-cc tumor, and for 80-cc or smaller prostates with a 3-cc tumor. While tumor size is unknown in a patient, one can use the patient's PSA and known linkages between PSA and tumor volume to choose a surrogate tumor volume for the purpose of applying the model.

These findings suggest that a reduction in prostate volume from 5ARI therapy could lead to increased detection of prostate cancer, including high-grade tumors, an observation that may define a role for these agents in assisting prostate cancer diagnosis. A similar detection bias can be expected in the REDUCE study, with the effect of the greater number of biopsy cores counterbalancing the larger baseline prostate volume.

REFERENCE

1. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med.* 2003;349:215-224.

■ DOES PROSTATE CANCER START WITH A MUTATION THAT UNLEASHES A VIRAL INFECTION?

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For several years, an emerging hypothesis about prostate cancer pathogenesis has gradually gained momentum from investigations exploring the possible contributions of inflammation and infection to the disease process. One particularly promising line of work has focused on RNaseL, an antiviral gene that plays a key role in the innate immune response to viral infections.

In vivo, activation of RNaseL by viral infection and endogenous interferon inhibits viral spread by degrading single-stranded RNA, thus directly preventing viral replication, and secondarily by causing the infected host cell to undergo apoptosis. Preclinical studies have shown that mice deficient in RNaseL are more susceptible to viral infection.

In humans, there is evidence that allelic variants of the RNaseL gene may increase the risk of developing prostate cancer. In particular, in a large epidemiologic study, men who were heterozygous (RQ genotype) for a single amino acid change from arginine to glutamine at position 462 had about a 50% greater risk of prostate cancer, and men homozygous at this locus (QQ genotype) carried a 2-fold higher risk compared with wild type (RR genotype).¹ The observation that variants in an antiviral gene predispose men to prostate cancer led to our investigation for a viral etiology for this disease.

In order to test this hypothesis, we used a powerful tool known as the ViroChip.² The ViroChip contains highly conserved sequences from all known viruses (almost 1000 in total) in the plant, animal, and human kingdoms. Hybridizing RNA from biological samples (such as respiratory secretions or tissue) to the chip allows determination of what expressed viral genes are present in the sample, identification of which family of viruses they belong to, and cloning and identification of the exact sequence of the viruses.² We hybridized RNA from the peripheral zone of radical prostatectomy specimens from men with prostate cancer who were genotyped for allelic variants at the 462 position of the RNaseL gene. In the initial 19 men, we identified 8 with a novel retrovirus.³ Remarkably, 7 of the 8 men with the new virus, dubbed XMRV, were found to have the QQ genotype in the RNaseL gene.

We have since screened more than 150 men. Data analysis is not complete, but preliminary findings show that about half of the men with the QQ mutation test positive for XMRV, compared with only 1 among those who do not have this variant.

The virus that XMRV most closely resembles is the murine leukemia virus (MuLV), a virus that causes leukemia in mice. There are, however, important differences between XMRV and MuLV, including the fact that XMRV does not infect mice and has a deletion in the glyco-GAG leader sequence that helps determine its virulence.

Tissue localization studies have demonstrated that XMRV does not reside in the epithelium, but in fibroblasts adjacent to the cancer. We hypothesize that the virus is somehow exerting an effect on the tumor by means of paracrine mechanisms, or through an indirect effect by providing an appropriate microenvironment to recruit macrophages and white blood cells that result in oxidative stress. Both of these hypotheses are currently under study. While a direct link between XMRV as a cause of prostate cancer remains to be proven, this work represents an exciting new finding in the possible pathogenesis of prostate cancer.

REFERENCES

1. Casey G, Neville PJ, Plummer SJ, et al. RNASEL Arg462Gln variant is implicated in up to 13% of prostate cancer cases. *Nat Genet.* 2002;32:581-583.
2. Wang D, Urisman A, Liu YT, et al. Viral discovery and sequence recovery using DNA microarrays. *PLoS Biol.* 2003;1:257-260.
3. Urisman A, Molinaro RJ, Fischer N, et al. Identification of a novel gammaretrovirus in prostate tumors of patients homozygous for R462Q RNASEL variant. *PLoS Pathog.* 2006;2:0211-0225.

■ MINIMALLY INVASIVE OPTION FOR BPH: TRANSURETHRAL NEEDLE ABLATION

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For men who want to avoid surgery or the need for ongoing medical treatment and its potential side effects, minimally invasive therapies for benign prostatic hyperplasia (BPH) offer an effective and potentially attractive alternative. Among currently available minimally invasive modalities, transurethral needle ablation (TUNA) has accumulated an extensive clinical experience.

Use of TUNA to treat BPH has its basis in 3 key principles of tissue interaction: absorption, scatter, and transmission. Energy is absorbed by tissue, forming heat at an atomic level. The energy is deflected (scattered) by tissue, causing directional change. Energy dissipates as it is conducted through tissue (transmission).

TUNA works by delivering radiofrequency (RF) energy into prostate tissue while small shields help to protect the urethra. The energy devascularizes and denervates prostatic tissue, creating necrotic lesions. The treatment effect is determined by the amount of tissue contact, the length of the needle, and the power (wattage). The RF energy decreases prostate size by 10% to 15% by means of heat and dehydration.

General criteria for patient selection include the feasibility to treat all lobes of the prostate; an American Urological Association symptom score >13; a maximum flow rate (Q_{max}) >4 mL/s; symptom duration >3 months; prostate size >15 g; and American Society of Anesthesiologists (ASA) surgical risk classification I-IV.

Among exclusion criteria is the presence of urethral strictures or active infection. The procedure also is contraindicated in patients with cardiac pacemakers, implantable cardiac defibrillators, and prostate or bladder cancer. Additional exclusion criteria include a history of neurogenic or atonic bladder; use of neural stimulators; bleeding disorders or current use of anticoagulants; ASA risk classification V; prior treatment with another minimally invasive technique or transurethral resection of the prostate (TURP); and extremes in gland size (<15 g, >100 g).

A typical procedure is preceded by administration of local agents 60 minutes beforehand, including an oral analgesic, oral sedative, nonsteroidal anti-inflammatory drug, antibiotics, and anticholinergics. Twenty minutes before the scheduled time of the procedure, the patient's bladder should be emptied with a catheter, followed by instillation of 40 to 60 cc of cold liquid lidocaine into the bladder.

Preprogrammed settings for the RF generator include a lesion time of 3 minutes, target temperature of 110°C (lesion core), and a urethral temperature of <43°C. Evaluation by transurethral ultrasound determines the needle insertion depth, and the TUNA system automatically calculates the needle length.

TUNA and TURP were compared in a randomized clinical trial involving 152 patients with BPH associated with a prostate volume

of 20 to 88 mL (mean of 43.3 mL). TURP was associated with a 57% incidence of ejaculatory disorder, compared with no such incidence in any patient treated with TUNA. No patient in the TUNA group required transfusion, compared with 10.5% in the TURP group. Urethral stricture and bladder neck obstruction each occurred in 2.6% of TURP patients, whereas 1.3% of TUNA patients developed stricture. Length of hospital stay with TUNA was less than half that of TURP (1.2 vs 3.5 days). The failure rate with TUNA was 3.9% in the first year and 2.6% for Years 2 to 5. One TURP patient (1.3%) required repeat resection during the second year.¹

Investigators in another study randomized 121 men with lower urinary tract symptoms (LUTS) secondary to BPH to TUNA or TURP and followed them for 5 years. Compared to baseline values, both TURP and TUNA led to significant improvement in the International Prostate Symptom Score, quality of life, and peak urinary flow rate that was retained during Years 1 to 5. Postvoid residual urine was significantly improved every year in the TURP group and in Year 5 in the TUNA group. TURP patients had a 41% incidence of retrograde ejaculation, compared with no incidence in TUNA patients. Erectile dysfunction, incontinence, and stricture formation also occurred more often with TURP than with TUNA.²

Cost virtually always rears its head during the assessment of a therapy or new technology, and TUNA is not exempt from that consideration. Treatment costs over 5 years were compared for medical therapy of BPH and for TUNA. The analysis considered monotherapy with the alpha-blocker tamsulosin or finasteride and combination therapy with an alpha-blocker and a 5-alpha-reductase inhibitor. The estimated cost of TUNA over 5 years was \$4811, compared with \$3485 for tamsulosin and \$4867 for finasteride (based on pregeneric era costs). Combination medical therapy was the most expensive treatment over 5 years, and TUNA's cost became equal to that of combination therapy after 2 years and 7 months.³

In summary, minimally invasive therapy in the form of TUNA offers a degree of symptom relief that is intermediate between medical therapy and TURP. TUNA has a lower complication rate compared with TURP. Failure to respond to TUNA does not preclude a subsequent TURP procedure. TUNA's 5-year cost compares favorably with 5 years of medical therapy.

REFERENCES

1. Chandrasekar P, Viridi JS, Kapasi F. Transurethral needle ablation of the prostate (TUNA) in the treatment of benign prostatic hyperplasia: a prospective, randomized study, long term results. *J Urol*. 2003;169(suppl):468. Abstract 1754.
2. Hill B, Belleville W, Bruskewitz R, et al. Transurethral needle ablation versus transurethral resection of the prostate for the treatment of symptomatic benign prostatic hyperplasia: 5-year results of a prospective, randomized, multicenter clinical trial. *J Urol*. 2004;171:2336-2340.
3. Naslund MJ, Carlson AM, Williams MJ. A cost comparison of medical management and transurethral needle ablation for treatment of benign prostatic hyperplasia during a 5-year period. *J Urol*. 2005;173:2090-2093.

■ EVOLVING ISSUES IN THE MANAGEMENT OF BPH/LUTS

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During the past decade, the paradigm for medical management of benign prostatic hyperplasia (BPH) has undergone a sea of change. In response to new research, the development and approval of novel pharmaceutical and minimally invasive therapies, and the changing economic climate of healthcare financing, physicians have altered their approach to caring for patients with BPH.

The evolution of BPH management is continuous. One area that will influence clinical management is the association between bladder outlet obstruction (BOO) and overactive bladder (OAB).

Clearly, detrusor overactivity (DO, the presumed mechanism of OAB) and BOO coexist. In our experience with more than 2800 men ages 50 years and over who were evaluated for lower urinary tract symptoms (LUTS), 62% had urodynamic evidence of BOO, and 66% of those with BOO had concomitant DO.¹

Although the urodynamic finding of increased DO is thought to result in OAB symptoms, the link between OAB symptoms and urodynamic findings has been difficult to establish.^{2,3} Nevertheless, results from 2 independent studies have suggested a relationship between OAB-associated urge symptoms and urge incontinence associated with DO. In a study of 160 men with LUTS, 68% of whom had BOO and 46% had concomitant DO, urge incontinence correlated with the presence of DO on urodynamic evaluation.³ A separate study of 459 men showed that the presence of DO correlated with the perception of urge symptoms and quality of life on the International Prostate Symptom Score.⁴

Bladder contractions are primarily under the control of the parasympathetic nervous system via muscarinic cholinergic pathways. Consequently, drugs with antimuscarinic properties have become first-line therapy for OAB, a clinical practice supported by multiple studies. Yet, concern about worsening obstructive symptoms or causing acute retention has kept physicians from prescribing muscarinic receptor antagonists for men who might have concomitant BOO. Two studies have directly addressed the concern.

Investigators in a multinational clinical trial examined the safety of treating men with BOO and symptomatic DO with tolterodine. The study involved 221 men with OAB and uroodynamically verified BOO, randomized to tolterodine or placebo and followed for 3 months with urodynamic testing and monitoring of adverse events. The results showed no difference between tolterodine and placebo with respect to acute urinary retention or withdrawal because of adverse events. Tolterodine significantly improved maximum flow rate, detrusor pressure at maximum flow, and postvoid residual (PVR) compared with placebo.⁵

The second study evaluated the combination of tolterodine and the alpha-blocker tamsulosin in 50 men with BOO and concomitant DO. All the men received tamsulosin; half were randomly assigned to receive concomitant tolterodine. Both groups had a statistically significant increase in flow rate and volume at first unstable contraction, and both groups exhibited a trend toward reduced PVR. Combination therapy significantly increased bladder capacity, reduced maximum unstable contraction pressure, and increased volume at first unstable contraction compared with tamsulosin alone. No patient in either group experienced acute urinary retention during 3 months of treatment.⁶

More recently, tolterodine extended-release was evaluated in 43 men with LUTS who had failed alpha-blocker therapy. After 6 months of treatment, the mean American Urological Association (AUA) symptom score decreased from 17.3 to 11.2, PVR decreased from 97 to 75 mL, daily frequency decreased from 9.8 to 6.3 voids, nocturia decreased from 4.1 to 2.9 episodes nightly, and maximum flow rate increased from 9.8 to 11.7 mL/s. No patient developed urinary retention.⁷

To date, no published randomized, controlled studies have described the effects of other anticholinergics. Prospective studies of extended-release formulations of anticholinergics in men with DO and BOO would be informative.

Another issue that will be likely to influence clinical management of BPH and urinary symptoms relates to the relationship between sexual function and LUTS. The prevalence of BPH,

LUTS, and sexual dysfunction increases with age. Recent studies have focused increased attention on the relationship between LUTS and sexual function. For example, the Cologne Male Survey found that 72.2% of men with BPH/LUTS had concomitant erectile dysfunction.⁸

Several lines of evidence have indicated that some of the same pathophysiologic mechanisms underlie BPH/LUTS and sexual dysfunction. Norepinephrine is the primary anti-erectile neurotransmitter. Alpha-adrenergic receptors are present in the human corpus cavernosum tissue, the majority being alpha-1A receptors.⁹ Blockade of alpha receptors has the potential to produce retrograde ejaculation, which is a class effect of alpha-adrenergic blockers.¹⁰

Although sexual activity normally diminishes with age, impaired sexual performance remains an undesirable effect of BPH, and treatment of BPH often results in significant improvement in sexual function.¹¹ Several other potential common pathophysiologic mechanisms between LUTS and erectile dysfunction have been suggested, including age-related atherosclerosis.

Treatment with alpha-blockers has been reported to improve sexual quality of life in men with BPH/LUTS.¹² Alpha-blockers can be used concomitantly with type 5 phosphodiesterase (PDE-5) inhibitors. In addition, 5-alpha reductase inhibitors, used increasingly to treat enlarged prostate, can be used safely in conjunction with PDE-5 inhibitors. At the 2006 AUA meeting, 3 separate reports demonstrated the safety and efficacy of PDE-5 inhibitors in men with LUTS and sexual dysfunction.¹³⁻¹⁵

REFERENCES

- Kaplan SA, Bowers DL, Te AE, Olsson CA. Differential diagnosis of prostatism: A 12-year retrospective analysis of symptoms, urodynamics and satisfaction with therapy. *J Urol*. 1996;155:1305-1308.
- Abdel-Aziz KF, Lemack GE. Overactive bladder in the male patient: bladder, outlet, or both? *Curr Urol Rep*. 2002;3:445-451.
- Hyman MJ, Groutz A, Blaivas JG. Detrusor instability in men: correlation of lower urinary tract symptoms with urodynamic findings. *J Urol*. 2001;166:550-553.
- Wadie BS, Ebrahim el-HE, Gomha MA. The relationship of detrusor instability and symptoms with objective parameters used for diagnosing bladder outlet obstruction: a prospective study. *J Urol*. 2002;168:132-134.
- Abrams P, Kaplan SA, De Koning Gans HJ, Millard R. Safety and tolerability of tolterodine for the treatment of overactive bladder in men with bladder outlet obstruction. *J Urol*. 2006;175:999-1004.
- Athanasopoulos A, Gyiopoulou K, Giannitsas K, Fisis J, Perimenis P, Barbalius G. Combination treatment with an alpha-blocker plus an anticholinergic for bladder outlet obstruction: a prospective, randomized, controlled study. *J Urol*. 2003;169:2253-2256.
- Kaplan SA, Walmsley K, Te AE. Tolterodine extended release attenuates lower urinary tract symptoms in men with benign prostatic hyperplasia. *J Urol*. 2005;174:2273-2276.
- Braun MH, Sommer F, Haupt G, Mathers MJ, Reifenrath B, Engelmann UH. Lower urinary tract symptoms and erectile dysfunction: co-morbidity or typical "Aging Male" symptoms? Results of the "Cologne Male Survey." *Eur Urol*. 2003;44:588-594.
- Traish AM, Netsuwan N, Daley J, Padman-Nathan H, Goldstein I, Saenz de Tejada I. A heterogeneous population of alpha-1 adrenergic receptors mediates contraction of human corpus cavernosum smooth muscle to norepinephrine. *J Urol*. 1995;153:222-227.
- Höfner K, Claes H, De Reijke TM, Folkestad B, Speakman MJ; European Tamsulosin Study Group. Tamsulosin 0.4 mg once daily: effect on sexual function in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. *Eur Urol*. 1999;36:335-341.
- Francisca EA, d'Ancona FC, Meuleman EJ, Debruyne FM, de la Rosette JJ. Sexual function following high energy microwave thermotherapy: results of a randomized controlled study comparing transurethral microwave thermotherapy to transurethral prostatic resection. *J Urol*. 1999;161:486-490.
- Kaplan SA. Use of alpha-adrenergic inhibitors in treatment of benign prostatic hyperplasia and implications on sexual function. *Urology*. 2004;63:428-434.
- Roehrborn CG, McVary KT, Kaminetsky JC, et al. The efficacy and safety of tadalafil administered once a day for lower urinary tract symptoms (LUTS) in men with benign prostatic hyperplasia (BPH). *J Urol*. 2006;175(suppl):527. Abstract 1636.
- McVary KT, Camps J, Henry GD, Conner SD, Tseng LJ, Van Den Ende G. Sildenafil improves erectile function and urinary symptoms in men with erectile dysfunction and concomitant lower urinary tract symptoms. *J Urol*. 2006;175(suppl):527. Abstract 1637.
- Kaplan SA, Gonzalez RR, Ogiste J, Te AE. Combination of an alpha-blocker, alfuzosin SR and a PDE-5 inhibitor, sildenafil citrate is superior to monotherapy in treating lower urinary tract symptoms (LUTS) and sexual dysfunction. *J Urol*. 2006;175(suppl):528. Abstract 1638.

1. In the Prostate Cancer Prevention Trial (PCPT), treatment with finasteride:

- Increased the overall risk of prostate cancer and the risk of high-grade cancer
- Decreased the overall risk of prostate cancer but was associated with an increased risk of high-grade cancer
- Had no significant effect on prostate cancer risk
- Demonstrated a trend toward a reduced risk of high-grade prostate cancer

2. The primary objective of the ongoing REDUCE clinical trial is to:

- Compare the relative effect of finasteride and dutasteride on prostate cancer risk
- Compare dutasteride and vitamin E for reducing prostate cancer risk
- Evaluate the effect of dutasteride on prostate cancer risk in men who have no clinical or pathologic evidence of prostate cancer
- Evaluate the effect of dutasteride on prostate cancer risk in men who have a clinical indication for prostate biopsy

3. The study reported by Briganti and colleagues showed that:

- Large prostates have more favorable tumor characteristics
- Prostate volume does not influence detection of prostate cancer
- Prostate volume does not influence detection of high-grade prostate cancer
- Small prostates have more favorable tumor characteristics

4. The study by Serfling and coworkers showed that:

- More biopsy cores are required to detect tumors in larger prostates
- Fewer biopsy cores are required to detect tumors in small prostates
- Treatment with finasteride necessitates a larger number of biopsy cores to detect prostate cancer
- All of the above
- a and b

5. Which of the following statements best describes the relationship between bladder outlet obstruction and overactive bladder (OAB)?

- The 2 conditions rarely co-occur.
- Both conditions result from detrusor overactivity.
- The 2 conditions often occur together.
- Neither of the conditions has an appreciable effect on quality of life.

6. Which of the following statements is true?

- Tolterodine has been shown to improve OAB symptoms in men.
- Type 5 phosphodiesterase inhibitors have been shown to improve BPH and lower urinary tract symptoms.
- Treatment of BPH can improve both urinary symptoms and sexual dysfunction.
- All of the above

7. What is XMRV?

- A gammaretrovirus that may be implicated in prostate cancer pathogenesis
- A new generation of laser for treatment of BPH
- A candidate pharmacologic agent for prostate cancer prophylaxis
- A virus created in the laboratory to examine potential infectious causes of prostate cancer

8. Which of the following statements is not true of transurethral needle ablation (TUNA)?

- Causes fewer adverse effects compared with transurethral resection of the prostate
- Involves the use of radiofrequency energy to create necrotic lesions on the prostate
- May have application in the treatment of prostate tumors located near the surface of the gland
- Appears to confer little or no risk of ejaculatory disorders

9. An economic assessment of TUNA showed that this minimally invasive technique:

- Is significantly more expensive than pharmacologic therapy for BPH over a 5-year period
- Is less expensive than all currently available forms of pharmacologic therapy for BPH
- Costs about the same as TURP when patients are followed for 5 years
- Compares favorably with 5 years of pharmacologic treatment with finasteride or the combination of an alpha-blocker and a 5-alpha-reductase inhibitor (5ARI)

10. Which of the following statements is most accurate?

- Treatment with a 5ARI represents a promising option for reducing the risk of prostate cancer.
- Laboratory studies suggest that 5ARIs have the potential to cause prostate cancer.
- Investigation of prostate cancer chemoprevention with 5ARIs is unlikely to continue because of concern aroused by the PCPT results.
- The combination of an alpha-blocker and a 5ARI shrinks the prostate to a greater extent than a 5ARI alone, increasing the likelihood of prostate cancer detection.

CME EVALUATION AND POSTTEST ANSWER KEY

CME Supplement to *Urology Times* • September 2006

LAST REVIEW DATE: August 15, 2006

RELEASE DATE: September 1, 2006

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