Advances in the Medical Treatment of Prostate Cancer, Bladder Cancer, Renal Cell Cancer, and Benign Prostatic Hyperplasia

Highlights from the XVIIth Congress of the European Association of Urology, Birmingham, UK, February 23-26, 2002

[*Rev Urol.* 2003:5(2):90–110]

Key words: Alfuzosin • Bacille Calmette-Guerin • Benign prostatic hyperplasia • Bicalutamide • Bladder cancer • Dutasteride • Finasteride • Lower urinary tract symptoms • Nomograms • Permixon • Prostate cancer • Prostate-specific antigen • Radical nephrectomy • Radical prostatectomy • Renal cell cancer • Tamsulosin • Transrectal ultrasound-guided biopsy • Virtual cystoscopy

Following is a review of noteworthy abstracts focusing on prostate cancer, bladder cancer, renal cell cancer, and benign prostatic hyperplasia, that were presented at the XVIIth Congress of the European Association of Urology.

Prostate Cancer

Prostate-Specific Antigen and Derivatives

Ulmert and colleagues[1] studied archival material regarding aspects of stability and grade of degradation in free prostate-specific antigen (fPSA) and total prostate-specific antigen (tPSA) in serum and ethylenediaminetetraacetic acid (EDTA)-plasma samples that had been stored for 25 years at −20°C. A total of 126 serum and 98 EDTA-plasma samples were randomly selected from a population study that included 22,439 men. Patients diagnosed with prostate cancer were excluded from the study. Age-matched controls obtained from a screening study in Gothenburg, Sweden, were collected, separated from blood cells, immediately frozen at −20°C, and analyzed within 10 days. Results demonstrated that analyses of fPSA and tPSA levels in archival EDTA-plasma, stored for 25 years at −20°C, are not significantly different from those in freshly collected samples and could be used for retrospective studies.

Complex PSA (cPSA) assays have been recently introduced as new tools for early prostate cancer detection in patients with low (2.5–4.0 ng/mL) and intermediate (4.0–10.0 ng/mL) PSA levels. Djavan and associates[2] conducted a prospective, multicenter European study that included a total of 477 men. Biopsy outcomes were correlated to the following parameters: serum tPSA, complexed PSA (Bayer Corporation, Westhaven, CT), PSA density (PSAD), PSA transition zone

Reviewed by Christian Seitz, MD, Mesut Remzi, MD, and Bob Djavan, MD, PhD, University of Vienna, Vienna, Austria; Claus G. Roehrborn, MD, FACS, Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX

(PSA-TZ), complex PSAD (cPSAD), complex PSA-TZ (cPSA-TZ), complex/total PSA (c/t PSA) ratio, complex/free PSA (c/f PSA) ratio, and free/total PSA (f/t PSA) ratio. In addition to standard statistics, an artificial neural network (ANN) was used in the analysis. In the intermediate PSA range (4.0–10.0 ng/mL), the performance of cPSA alone was identical to tPSA, whereas the c/t PSA ratio and cPSA-TZ significantly improved cancer detection. In this PSA range, c/t PSA was slightly superior to f/t PSA, even when an ANN was employed. In contrast, cPSA and the c/t PSA ratio outperformed other parameters in the low PSA range (2.5–4.0 ng/mL). Djavan and associates concluded that cPSA and cPSA indices improve cancer detection in patients with PSA levels from 4.0 ng/mL to 10.0 ng/mL. Their foremost advantage is, however, a significant improvement of prostate cancer detection in patients with PSA levels from 2.5 ng/mL to 4.0 ng/mL.

Screening, Epidemiology, and Prevention

Rowe and colleagues,[3] from London, UK, evaluated the use of free-to-total PSA ratio measurements in a group of 426 men aged 50–65 years who were participating in a screening program. All men with a tPSA above 4.0 ng/mL or with a PSA between 1.1 ng/mL and 4.0 ng/mL with a free/total ratio of less than 20% underwent biopsy. The overall cancer detection rate in this study was 3.52% (15/426). Sixty-one men had a PSA between 1.1 ng/mL and 4.0 ng/mL and a free/total ratio < 20%. Of these, 8.2% (5/61) had prostate cancer detected upon biopsy. All of these cancers were clinically localized. The use of free/total PSA ratios may provide a means of detecting organ-confined prostate cancer in young men who would benefit from curative treatment when the total PSA is between 1.1 and 4.0 ng/mL. This selected small group of men may be the best candidates for minimally invasive treatments, such as laparoscopic radical prostatectomy, nerve-sparing prostatectomy with preservation of negative margins, and prostate brachytherapy.

These results demonstrate that small prostate cancers with low PSA levels and small tumor volumes show all the features of prostate cancers with higher tumor volumes and fulfill the criteria of malignant cancers.

Bartsch and associates[4] conducted a seven-site prospective evaluation of the Bayer complexed PSA (cPSA) assay in the early detection of prostate cancer. Their objective was to compare the clinical performance of cPSA with tPSA and PSA ratios (% fPSA, % cPSA) as a first-line test for prostate cancer detection. They also sought to determine whether additional diagnostic parameters would improve the diagnostic performance over the tPSA measurement. A total of 732 patients scheduled for prostate biopsy were enrolled prospectively at each of the seven sites and were evaluated. The authors found that cPSA provided a better diagnostic performance than did tPSA, and cPSA as a single test provided improved specificity over tPSA. The use of % fPSA and % cPSA offered little or no additional benefit in the differentiation of benign and malignant disease over cPSA at clinically relevant tPSA concentrations.

Vollger and coworkers[5] examined the characteristics of tumors detected in patients with low PSA levels; the tumors were found by including men with PSA levels of 1.25–3.25 ng/mL and a free-to-total ratio of < 18% among those biopsied. Although no men with a PSA between 0.00 ng/mL and 1.99 ng/mL had tumors with positive margins, positive margins were present in 4.2% of tumors in men with levels 2.00–3.99 ng/mL. They also found that at low PSA levels, 65% of the lesions showed multifocality and, in 36% of the patients, there was tetraploid DNA distribution. These results demonstrate that small prostate cancers with low PSA levels and small tumor volumes show all the features of prostate cancers with higher tumor volumes and fulfill the criteria of malignant cancers: they are multifocal, show tetraploidy and, independent of their size, exhibit high proliferative activity.

Multifocal Disease

Prostate cancer is a heterogeneous, multifocal disease exhibiting a variety of clinical and morphologic manifestations. Multifocal disease is found in about 90% of all cases presenting with total PSA levels around 10.0 ng/mL at the time of diagnosis.

The aim of a study by Horninger and colleagues[6] was to evaluate whether prostate cancers with low tumor volumes and total PSA levels below 4.0 ng/mL were also multifocal. The authors included a total of 80 prostate cancer patients with preoperative PSA levels below 4.0 ng/mL who had participated in the Tyrol PSA Mass Screening Project. Of the 80 patients, 28 (35%) had unifocal prostate cancers, whereas 52 (65%) had multifocal lesions. Similar to studies of prostate cancers with PSA levels of about 10.0 ng/mL, their study showed that a high percentage of prostate cancers with PSA levels below 4.0 ng/mL and small tumor volumes exhibited multifocal lesions.

The cancers diagnosed among

nonparticipants in PSA screening may have a substantial impact on the effectiveness of screening at the population level. Mäkinen and associates,[7] therefore, considered this in the comparison of cancers diagnosed in the Finnish PSA screening trial. From 1996 to 1998, a total of 24,000 men were randomized to the screening arm, and the remaining 35,973 men formed the control arm. Cancers diagnosed within 12 months of blood sampling were regarded as screen-detected. Information on cases diagnosed among the nonattenders and in the control arm was obtained through a record-linkage with the Finnish Cancer Registry with a follow-up of 12 months from randomization. They found a detection rate of 2.4% (369/15,685) among those screened, whereas 0.5% (36/7047) of the nonparticipants in the screening and 0.3% (111/35,973) of the controls were diagnosed with prostate cancer. A vast majority—85% (313/369)—of the screen-detected cancers were clinically localized. The proportion of localized tumors was 58% (21/36) among the nonattenders ($P < .01$) and 63% (70/111) among the controls ($P < .01$). More than 50% of the screen-detected cancers, as well as of the cancers diagnosed outside an organized screening, were moderately or poorly differentiated (World Health Organization [WHO]). The median PSA among those screened was 7.1 ng/mL; it was significantly higher among the nonattenders (16.1 ng/mL) and controls (13.2 ng/mL). This study showed that PSA screening increases the diagnosis of early-stage prostate cancer. The present screening trials must be assessed according to initial randomization to avoid a possible bias resulting from "a healthy screened effect."

Nonsteroidal Anti-Inflammatory Drugs

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) have been reported to protect against the development of colorectal cancer. NSAIDs and finasteride inhibit the growth of human prostate cancer cell lines in vitro. Promising findings concerning the potential value of finasteride and NSAID agents in the prevention of prostate cancer were reported by Irani and coworkers.[8] The aim of their study was to examine the relationship of these medications to the risk of prostate cancer in a prostate biopsy-based, case-control study. The study included 639 patients with prostate cancer and 659 cancer-free controls from 12 French centers. Univariate analysis showed no significant impact of aspirin and finasteride on the risk of prostate cancer, whereas the nonaspirin NSAID users had a lower risk (odds ratio [OR], 0.80; 95% confidence interval [CI], 0.64-0.99). After adjusting for potential confounders, the protective effect of nonaspirin NSAIDs was no longer significant (OR, 0.84; 95% CI, 0.66-1.07), whereas finasteride showed a significant protective effect (OR, 0.58; 95% CI, 0.37-0.92). Their results suggest that finasteride could play a chemopreventive role in prostate cancer. Although aspirin did not show any impact on the risk of prostate cancer, the role of nonaspirin NSAIDs warrants further study.

Although aspirin did not show any impact on the risk of prostate cancer, the role of nonaspirin nonsteroidal anti-inflammatory drugs warrants further studies.

Family History

A positive family history (FH) is an important risk factor for prostate cancer, and several studies have been conducted on screening in high-risk families. However, few data are available concerning PSA levels in unaffected relatives in those families. Valeri and colleagues[9] assessed future prostate-cancer risk in unaffected relatives by demonstrating higher PSA values in high-risk families. A screening program (PSA testing) was conducted in 637 first-degree relatives (brothers or sons), aged 40–70 years, of prostate cancer patients in three French urological centers. Of these 637 unaffected relatives, 92 were eligible for this study: PSA ≤ 4.0 ng/mL and aged 60–70 years. A control population (consecutive men during the same period) was obtained from the screening departments of French public health centers: men without a family history of prostate cancer, aged 60–70 years, and a PSA of ≤ 4.0 ng/mL. For each age group, mean PSA levels were significantly higher in men with a positive FH than in controls. Moreover, the age-adjusted PSA level was significantly higher in men with a positive FH than in controls. The investigators concluded that unaffected men with an FH of prostate cancer have higher PSA levels than do controls, supporting the evidence that first-degree relatives of prostate cancer patients are at high risk.

Detection and Treatment of Prostate Cancer in Germany

Prostate cancer is a considerable health problem in Germany, with 28,000 newly detected cases and 13,000 deaths per year. Moreover, mortality has increased over the last 10 years. Currently, early-detection programs within the German health care system rely on digital rectal examination (DRE) only. PSA screen-

ing is not included, and no evidence-based guidelines exist that summarize the present state of knowledge.

The German Society of Urology developed a consensus paper about early prostate cancer detection. Luboldt and associates[10] published a paper describing the consensus development of evidence-based guidelines in Germany. This group invited national and international experts (including urologists, internists, laboratory physicians, pathologists, and technicians) to participate with patients in developing guidelines based on the level of evidence ranked according to the Scottish Intercollegiate Guidelines Network (SIGN). Among ten summary recommendations was the statement that PSA should be measured only after full information on the implications of the test results for biopsy and treatment have been provided to the patient.

The U.S. Department of Defense Center for Prostate Disease Research (DoD-CPDR) database contains over 300,000 clinical records of transrectal ultrasound (TRUS), biopsy, medical history, primary staging, radical prostatectomy pathology, annual questionnaires, and necropsy reports, and offers a valuable source of data for research projects. The DoD-CPDR database was developed to 1) standardize clinical procedures for prostate cancer patients; 2) support retrospective and prospective research on prostate cancer, clinical trials, clinical management, training, and education; and 3) integrate information from clinical, tissue sampling, and basic science research projects. As of July 2001, the database has archived 307,931 clinical records on 13,878 men. Treatment modalities were employed as follows: radical prostatectomy, 41.7% (4234 men); external beam radiation, 42.2% (4286 men); brachytherapy, 4.0% (401 men); and cryotherapy, 0.3% (26 men). The ratio of death from prostate cancer versus death from another cause was 28.2%. In radical prostatectomy patients, 1-year, disease-free survival has improved significantly since 1995. On the basis of these data, Leon and colleagues[11] reported that radical prostatectomy is currently the most common treatment modality for German military men with prostate cancer. More than two thirds of patient mortality results from non-prostate causes.

The authors concluded that Entonox is a safe, fast-acting, effective form of analgesia that should be used routinely during prostatic biopsy; it also causes significantly less pain compared with standard rectal local anesthetics.

Prostate Biopsies

TRUS-guided prostate biopsy is routinely performed as a day-case procedure without sedative analgesia and, in some centers, without any local analgesia. There is evidence, however, suggesting that the procedure is regarded by patients as uncomfortable and even painful. In a randomized, controlled, double-blind study, Massood and associates[12] evaluated the effectiveness of Entonox (50% nitrous oxide and oxygen) as analgesia. Ninety-six men, none of whom had a previous biopsy or had a serious concomitant illness, were randomized to receive either Entonox or air only via a breath-activated device. At the end of the procedure, patients completed a questionnaire composed of a visual analogue pain scale (range, 0–10). Fourteen patients who declined the study also completed the visual analogue pain scale (to assess the placebo effect of using a mask). All patients were contacted 1 week later to assess any persisting side effects. Statistical analysis was performed using a one-way analysis of variance (ANOVA) test.

A total of 110 patients were studied. The ANOVA test showed a highly significant difference between the three groups: $F(2,107) = 73.348$; $P < .001$. This difference was found between the Entonox and air groups, as well as the Entonox and placebo groups. There was no significant difference between the air and the placebo groups. There was also no significant correlation between age and pain or prostate size and pain. Of the 51 patients in the Entonox group, 7 complained of drowsiness, which settled at the end of the procedure. Moreover, 49 of these patients said they would be happy to undergo this procedure again, if required; 2 patients said they would prefer some added analgesia. Of the 45 patients in the group receiving air, 2 had their procedure abandoned because of pain. Another 19 of these patients would prefer to have more analgesia if the procedure were to be repeated; 2 patients said they would prefer a general anaesthetic next time. The authors concluded that Entonox is a safe, fast-acting, effective form of analgesia that should be used routinely during prostatic biopsy; it also causes significantly less pain compared with standard rectal local anesthetics.

Nambirajan and colleagues[13] also performed a prospective, randomized study of the role of periprostatic local anesthesia to reduce discomfort during TRUS-guided biopsy. They investigated 50 men (mean age, 64.35 years; range, 47–74 years) undergoing TRUS biopsy for elevated PSA or abnormal DRE. The patients were randomized into local anesthetic

or placebo groups. An 18G needle was passed through the biopsy channel of the TRUS probe, and 5 mL of 1% lignocaine was infiltrated on either side of the prostate, 2.5 mL each in the base and apex of the prostate. In the placebo group, the needle was passed without injection of any material. Six to ten biopsy cores were taken, with the majority being ten. Patients filled in an expected pain score before the procedure to assess the element of anxiety involved. They also completed a Visual Analogue Score after the biopsy. In the local anesthesia group, the mean pain score was 3.1 ± 2.16, compared with 6.6 ± 2.5 in the placebo group. This difference was significant. Because the expected pain score was comparable in both groups, the level of anxiety did not account for the observed difference. When patients were asked whether they would undergo the procedure again, 100% of the local anesthesia group and only 64% of the placebo group responded "yes." This difference was statistically significant (P = .002 using the Fisher exact test). The authors concluded that a periprostatic local anesthetic with 1% lignocaine reduces discomfort significantly during TRUS biopsy, and they have promoted its routine use.

Otite and coworkers[14] evaluated the efficacy of 5% lignocaine ointment applied rectally for 30 minutes in 60 patients to improve their tolerance to TRUS-guided prostatic biopsy. Thirty minutes prior to TRUS, patients were randomized into two groups: one group of 29 patients received 15 g of 5% lignocaine ointment (LO) instilled rectally, and the other group of 31 patients received a similar amount of transonic jelly (no-LO). Sextant biopsies were taken, with additional biopsies guided by greyscale or Doppler abnormalities. Immediately after the procedure, the pain experienced during different stages of the procedure was assessed, based on a visual grading scale. The mean pain score was lower in the LO group (2.51) than in the no-LO group (2.91), but this was not statistically significant (P = .135). The tolerance of patients to TRUS-guided prostatic biopsy was not significantly improved with intrarectal 5% lignocaine ointment.

Repeat Prostate Biopsies

Remzi and colleagues[15] conducted a multicenter study in patients with low and intermediate PSA levels (2.0–10.0 ng/mL) to determine the influence of total and transition-zone (TZ) volumes of the prostate on whether one set of biopsies was sufficient to rule out prostate cancer or whether repeat biopsies were required. A total of 1018 patients underwent TRUS-guided needle sextant and two TZ biopsies of the prostate. Total and TZ volumes of the prostate were measured. All patients with benign disease on initial biopsy underwent repeat biopsies within 1–2 months. Of the 1018 patients, 344 (33.8%) had prostate cancer—285 (28%) on the first biopsy and 59 (8.1%) on the repeat biopsy. Compared with patients diagnosed with prostate cancer after the first set of biopsies, patients diagnosed after the second set had larger total prostate and TZ volumes (43.1 ± 13.0 mL vs 32.5 ± 10.6 mL, P < .0001, and 20.5 ± 8.3 mL vs 12.8 ± 6.0 mL, P < .0001, respectively). The analysis of positive first/repeat biopsy results showed that the probability of having a negative first and a positive repeat biopsy correlated with a greater TZ volume. The authors concluded that, whereas TZ volume has no impact on the outcome of the first biopsy, in patients with a TZ volume of 25 mL, a repeat biopsy should be considered in case of a negative first biopsy.

Complex PSA has been recently introduced as a new marker for early prostate cancer detection. Repeat biopsies are becoming part of routine practice because of their high cancer-detection rate. Djavan and associates[16] evaluated the value of this newly developed marker to predict the outcome of repeat prostate biopsies in a prospective, multicenter, European study that included a total of 447 men. As many as 33% were found to have prostate cancer, and 67% were found to have benign prostatic hypertrophy (BPH). The presence of prostate cancer was determined by using a TRUS-guided octant needle biopsy with a repeat biopsy at 6 weeks if no cancer was found. Serum PSA, % fPSA ratio, cPSA, cPSAD, cPSAD-TZ, c/t PSA ratio, c/f PSA ratio, PSAD, PSA-TZ, DRE, and PSA velocity were compared. In addition to standard statistics, an artificial neural network (ANN) was created, validated, and employed in the analysis with an advanced multiplayer perceptron selected for accuracy by a genetic algorithm. At 95% sensitivity for detecting prostate cancer on repeat biopsy, the analysis revealed the highest predictive value for c/t PSA and f/t PSA ratios and TZ volume, in declining order of importance. The combination of c/t PSA and TZ volume was highly predictive of cancer on repeat biopsy (sensitivity, 84.2%; specificity, 79.5%). The ANN constructed on the basis of all parameters mentioned above allowed a further

The probability of having a negative first and a positive repeat biopsy correlated with a greater transition-zone volume.

improvement by 33% of the positive predictive value and 41% of the negative predictive value. The ANN specificity (validation patients only) was 89%; % c/t PSA ratio, 52%; % fPSA ratio specificity, 40%; % TZ volume specificity, 34%; and % PSA-TZ density specificity, 30%. The respective receiver operating characteristic areas under the curve were 91.3%, 83.0%, 79.0%, 77.0%, and 73.0%. The optimal selection criteria for repeat biopsies still need to be identified. The authors concluded that c/t PSA ratio, % fPSA, and TZ volume are the most prominent biochemical selection parameters. The employment of highly predictive ANNs will replace standard cutoff and random selection for a more accurate identification of patients requiring repeat biopsies.

The authors concluded that erectile dysfunction is a significant complication after transperineal I-125 implantation of the prostate: 3 months after the operation, 48% of preoperative potent men developed erectile dysfunction that did not improve within the first year.

Localized Prostate Cancer (Nonsurgical Approach)

A randomized controlled comparison of the effectiveness of radical prostatectomy with that of external beam radiotherapy (EBRT) was conducted by Di Stasi and coworkers.[17] A total of 63 patients with clinically localized prostate cancer (clinical stage, T1-T2-T3a, N0, M0) were enrolled in a controlled, randomized trial. Thirty-one patients received radical prostatectomy, and 32 patients received EBRT. Diagnosis and clinical staging were performed with serum PSA, DRE, TRUS, prostatic biopsy, computed tomography (CT) of the abdomen and pelvis, x-ray of the chest, and bone scan. Acute and chronic side effects were recorded in both groups. All patients were followed every 3 months by a serum PSA and clinical examination and every 12 months with TRUS, chest x-ray, CT of the abdomen, and a pelvis and bone scan. After a mean follow up of 32.3 ± 6.6 months in the radical prostatectomy arm and 30.1 ± 9.7 in the EBRT arm, acute side effects were observed in 7 patients (22.5%) and 22 patients (68.7%), respectively. Chronic side effects were observed in 22 patients (70.9%) in the radical prostatectomy arm and 19 patients (61.3%) in the EBRT arm (P = .335). During follow-up, biochemical and/or organic relapse was observed in 12 patients (38.7%) in the radical prostatectomy arm and in 9 patients (28.1%) in the EBRT arm (P = .281). Disease-free survival was 22.8 ± 13.8 months in the radical prostatectomy arm and 22.7 ± 13.2 in the EBRT arm. Cause-specific survival was 97% in both groups. These preliminary results showed no statistical differences in cause-specific survival, chronic side effects, and disease-free survival in patients treated with radical prostatectomy or EBRT; however, EBRT caused more acute side effects.

Radiotherapy

Biochemical progression after radical prostatectomy can be caused by local recurrence or systemic disease. In patients with clinical findings suspicious of local recurrence, conformal radiotherapy is a recommended treatment option. Hammerer and colleagues,[18] from Hamburg, Germany, analyzed the toxicity and progression rate of this treatment. A total of 24 patients after radical prostatectomy who were found to have biochemical progression according to the American Society for Therapeutic Radiology and Oncology criteria, with TRUS and/or magnetic resonance tomography suspicious of local recurrence, were analyzed. In 13 patients, a biopsy-proven local recurrence was seen. Patients were aged 46–74 years. Progression occurred up to 152 months after surgery. The histopathologic tumor stage was pT2 in 7 cases, pT3 in 15 cases, and pT4a in 2 cases. Patients received conformal radiotherapy with total doses between 60 and 70 Gy at the reference point (ICRU 50), 1.8 Gy per fraction. A total of 21 patients received additional hormonal therapy. Radiotherapy was initiated 6 months to 155 months after surgery (mean, 45 months; median, 37 months). With a median follow-up of 26 months, all patients showed a decrease of PSA values after therapy. Five patients died, 4 of them by tumor progression. The calculated 5-year survival was 69%. The biochemical disease-free survival rates were 53% at 2 years and 38% at 5 years. Fourteen patients developed a secondary PSA elevation, 3 patients with local progressions, 3 patients with metastases, and 1 patient with a combined recurrence. Acute and late toxicity, classified with the Radiation Therapy Oncology Group (RTOG) score, was moderate, with only grade 1 or 2 toxicity. A PSA response could be seen in men with local recurrence after radical prostatectomy who were treated with conformal radiotherapy with minimal toxicity. In conclusion, long-term results showed that, in this selected group of patients, more than 60% developed progression.

Transperineal Brachytherapy

Van der Hoeven and associates,[19] from Leiden, The Netherlands, assessed erectile function in a prospective study of men with early-stage prostate cancer who underwent transperineal

brachytherapy with radioactive I-125. Transperineal implantation of radioactive I-125 causes fewer side effects to the bladder and rectum. A better chance of preserving potency is an important consideration for patients when they choose brachytherapy instead of radical prostatectomy for localized grade I or II prostate cancer. Patients were asked to fill out an International Index of Erectile Function (IIEF) preoperatively and at 3, 6, and 12 months after implantation. Sixty-five patients (93%) returned evaluable questionnaires. The total IIEF score (range, 5–75) of men who initially had no or mild erectile dysfunction decreased from 64.1 preoperatively to 51.6 at 3 months, 49.3 at 6 months, and 50.2 at 1 year. The authors concluded that erectile dysfunction is a significant complication after transperineal I-125 implantation of the prostate: 3 months after the operation, 48% of preoperative potent men had developed erectile dysfunction that did not improve within the first year.

To determine the safety and efficacy of performing a prostate seed implant in patients who had undergone a previous transurethral prostate resection (TURP), Stone and colleagues[20] investigated 665 men with T-T2 prostate cancer who received an I-125 or Pd-103 implant between 1989 and 1999; 49 (7.4%) of these patients had a history of TURP. No patients received supplemental EBRT. Their median age was 69 years and the median PSA level was 9.1 ng/mL. The clinical stage was T1b in 4 patients (8%), T1c in 19 (39%), T2a in 7 (14%), T2b in 14 (29%), and T2c in 5 (10%). The Gleason score was 2-4 in 11 patients (22%), 5-6 in 26 men (53%), and 7-9 in 12 men (25%). The mean follow-up on 47 men was 4.6 years. The mean time from TURP to seed implantation was 5.9 years. The median follow-up from implant was 4.6 years. The authors suggest that permanent prostate brachytherapy (real time method) with either I-125 or Pd-103 can be safely performed in men with a history of a prior TURP. Only 2 patients developed urinary incontinence during follow-up. In addition, PSA control rates were high, especially in those with low-risk cancers.

Palisaar and associates found that the presence of Gleason grade 4 or 5 cancer was the most important factor in determining the outcome of organ-confined prostate cancer treated with radical prostatectomy alone.

Losa and coworkers[21] prospectively evaluated urinary and sexual function in 100 patients with localized prostate cancer treated with palladium-103 brachytherapy. Using the International Prostate Symptom Score (IPSS), they found that, although there was an initial deterioration in urinary function, at 6 months following treatment there was no significant difference between pre- and post-treatment urinary scores. Sexual function was preserved in about 70% of patients; sildenafil was able to restore normal erections in 77% of patients with postoperative erectile dysfunction.

New Approaches to Radical Prostatectomy

Several attempts have been made to abandon pelvic lymphadenectomy (PLA) before radical prostatectomy in patients with certain preoperative findings. Hofer and colleagues[22] had previously shown that in patients with a PSA < 10 ng/mL, fewer than four positive biopsies, and a Gleason score < 7, the likelihood of positive lymph nodes is < 1%; therefore, PLA was not performed in these patients.

Hofer and colleagues[22] investigated whether performing PLA leads to a decrease in morbidity from radical prostatectomy. They compared intra-, peri-, and post-operative indicators in two groups of matched patients with pT2 and pT3 prostate cancers who underwent the operation. There were statistically significant reductions in operation time, intraoperative suction drainage volumes, and postoperative drainage duration in patients who did not undergo PLA. Among patients who had PLA, there was an increase in the incidence of lymphoceles/fluid retention, as diagnosed on ultrasound, requiring percutaneous drainage. There were, however, no differences in other postoperative complications, such as hemoglobin reduction, need for transfusion, hematoma, or wound infection. This study shows that not performing PLA in selected patients with defined preoperative parameters leads to a significant reduction in postoperative morbidity of radical prostatectomy.

Palisaar and associates[23] analyzed clinical and pathologic characteristics of 331 consecutive men with pT2N0 prostate cancer, treated solely with radical prostatectomy, to identify independent predictors of PSA failure. The importance of the Gleason score in determining whether men with organ-confined disease (pT2N0) subsequently suffer biochemical failure was illustrated. They found that the presence of Gleason score 4 or 5 cancer was the most important factor in determining the outcome of organ-confined prostate cancer treated with radical prostatectomy alone.

Fernandez and coworkers[24] achieved good results with the use of waterjet dissection during nerve-sparing radical prostatectomy. They compared the

results of 36 consecutive patients having bilateral, nerve-sparing radical prostatectomy, 18 of whom underwent waterjet dissection with Hydrojet (Erbe Elektromedizin GmbH; Tübingen, Germany) and the remainder of whom had the conventional procedure. Age, clinical stage, and prostate volume were comparable in both groups. The researchers found that use of the waterjet reduced blood loss by 36%, decreased the operation time by 20%, and improved outcomes with respect to potency. They also reported that the technique was safe, simple, and relatively easy to learn.

Laparoscopic Radical Prostatectomy

Guillonneau and colleagues[25] reported on 727 patients with clinically localized prostate cancer and candidates for radical prostatectomy who were successively operated upon in a single institution in Paris, France. The mean PSA level was 10.4 ng/mL (range, 1.5–55.0 ng/mL). The clinical stage was T1b in 3 patients, T1c in 449 men, T2a in 224 men, and T2b in 21 patients (TNM97). A pathologic examination was assessed, and positive margins were recorded. PSA recurrence was defined as PSA > 0.1 ng/mL and confirmed by a second rising PSA. Survival was calculated. Recurrence time was defined as the time with the first rising PSA. Results showed that midterm oncological follow-up (30–39 months) was satisfactory and compared well with conventional surgery.

Guillonneau and colleagues[26] also presented results from a study assessing the oncological risk of neurovascular bundle preservation during laparoscopic radical prostatectomy (LRP). They found that positive surgical margins during nerve-sparing laparoscopic prostatectomy correlates with both intra-fascial neurovascular bundle preservation and pathologic stage. According to the literature, the risk for progression is low, taking into account the rate and the length of the positive surgical margin.

Rassweiler and associates[27] have performed more than 300 LRP procedures using a transperitoneal combined ascending and descending technique (Heilbronn technique). They characterized the learning curve as on-going and enumerated the complications of this novel procedure, including rectal injury, difficult dissection, and bleeding at the dorsal vein complex. They analyzed their results in three groups of 100 patients to observe differences in outcomes as their experience increased. They found significant reductions in operating times, conversion rates, open reintervention, transfusion rates, and complication rates between the first and third groups, but there were no differences in rates of positive margins or in continence rates. With increasing experience, the incidence of complications decreased significantly in their series, requiring no conversion or reintervention in the last 50 cases. In contrast to other series, they observed a linear decrease of relevant parameters (ie, operative time) rather than an exponential decrease with a plateau after the initial 50 cases.

Roumeguere and coworkers[28] prospectively studied the impact of a pure extraperitoneal laparoscopic approach for radical prostatectomy on continence and potency. They performed 85 extraperitoneal LRPs. A total of 45 patients answered selected questions about their continence and sexual activity before the prostatectomy as well as 1 month, 3 months, 6 months, 9 months, and 1 year after the prostatectomy. Nerve-sparing technique was used in 17 patients. Among the respondents, continence was described as perfect in 14.3%, 33.3%, 52.8%, and 87.0% of patients at 1, 3, and 6 months, and 1 year, respectively. Among the 17 patients who underwent nerve-sparing surgery, there was a maintenance of spontaneous sexual activity in 17.6%, 23.5%, 29.4%, and 65.0% at these postoperative intervals; at 1 year, 64.7% of all respondents reported that sexual intercourse was possible.

With the introduction of robotically-assisted laparoscopy and promising results in cardiac surgery, the range of laparoscopic operative indications may expand in urologic surgery in the future.

Radical prostatectomy is a technically demanding reconstructive procedure. With the introduction of robotically-assisted laparoscopy and its promising results in cardiac surgery, the range of laparoscopic operative indications may expand in urologic surgery in the future.

Wolfram and colleagues[29] presented and assessed possible alternative robotically-assisted laparoscopic approaches. They used the telerobotic daVinci Surgical System (Intuitive Surgical Inc., Mountain View, CA) in 47 patients who underwent laparoscopic surgery for clinically localized prostate cancer. They found that the operation was feasible by either an intra- or extra-peritoneal approach and that, although both operative time and complication rates decreased over time, more experience was needed before the robotically-assisted procedure could become the standard approach.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI)

for local extension of prostate cancer and lymph node metastases is warranted for men at higher risk of metastases before considering radical radiotherapy. Boreley and associates[30] compared MRI with laparoscopic pelvic lymph node dissection (LPLND) for prostate cancer staging in 40 consecutive patients at high risk of locally advanced disease (on the basis of DRE, PSA 20 ng/mL, and Gleason score 7 biopsy) who had both a pelvic MRI and a subsequent LPLND for staging. Preoperative staging by MRI was compared with the histology of obtained lymph node specimens. LPLND was performed exactly as described by Clayman and colleagues.[31] All patients had a negative bone scan, and 11 of 40 patients (27.5%) had pelvic lymph node metastases confirmed by an LPLND. Of these, the MRI correctly identified 3 (27.3%) and missed 8 (72.7%). However, all suspicious lymph nodes on the MRI were confirmed histologically (100% positive predictive value). Laparoscopy and biopsy appeared to be a better staging modality. The MRI missed many lymph node metastases in "high-risk" patients being considered for radical treatment of prostate cancer. An LPLND allows significantly more accurate staging, providing for superior treatment planning, and should be considered an acceptable additional procedure.

Nomograms—Predicting the Outcome After Radical Prostatectomy

Two preoperative nomograms for the recurrence of prostate cancer after radical prostatectomy, based on readily available clinical variables, were developed by Kattan and colleagues[32] at Baylor College of Medicine and by D'Amico and associates[33] at Harvard Medical School. Calibration and validation of these tools were achieved using North American patient cohorts. Their validity has not yet been shown in patients from other continents. Graefen and coworkers[34] investigated the predictive accuracy of these nomograms when applied to European men with localized prostate cancer. The nomograms were applied to retrospective clinical data on patients who had undergone radical prostatectomy in Hamburg, Germany. Predictions of probability of freedom from recurrence at 2 and 5 years, as made by the nomograms, were compared with actual recurrence data from follow-up records. The two nomograms predicted recurrence with similar accuracy when applied to men diagnosed with localized prostate cancer in Germany. They concluded that these nomograms could be applied to non-U.S. patients.

Advanced Prostate Cancer

Because each Swedish citizen has a unique civic registration number, information in population-based registries can be matched, allowing for long-term follow-up. Steineck and colleagues[35] identified more than 126,000 men (in the Swedish Cancer Registry) with prostate cancer diagnosed between 1960 and 1997, and analyzed those 30,082 men who were orchidectomized in regard to the occurrence of fractures; castration is linked to osteoporosis and may cause fractures. Two control groups were used: prostate cancer patients without an orchidectomy and 631,190 population controls. The cause-of-death register gave the date of death or emigration, allowing calculations of person-time at risk. The relative risk (RR) of hip fractures among those orchiectomized, with 95% confidence interval, was 2.02 (range, 1.90–2.14) compared with population controls and 1.57 (range, 1.48–1.67) compared with prostate cancer patients. In looking at fractures that are not believed to be related to osteoporosis (the skull and face), the corresponding relative risks were 1.25 (range, 0.94–1.68) and 1.17 (range, 0.89–1.53). Unexpectedly, the increased relative risk for hip fractures was highest during the first year of follow-up (RR = 2.48), whereas after 5 years the relative risk was close to 1. The authors concluded that castration results in clinically significant osteoporosis-related fractures, the majority of which occur during the first 5 years after the procedure.

Castration is linked to osteoporosis-related fractures, the majority of which occur during the first 5 years after the procedure.

Recent results from a large international trial of early prostate cancer (EPC) therapy using bicalutamide (Casodex®, AstraZeneca, Wilmington, DE) were presented in two papers by Iversen and colleagues[36] and See and associates.[37] In this program, which is still ongoing, 8113 men from around the world, with nonmetastatic prostate cancer, have been recruited into three randomized, double-blind, placebo-controlled trials. In addition to one of three standard-care options (radical prostatectomy, radiotherapy, or watchful waiting), the men received either 150 mg bicalutamide daily or placebo once daily. Results reported in 2001 showed that, irrespective of the patient's lymph node status, bicalutamide, 150 mg/d, reduced the risk of objective disease progression and PSA doubling in patients with localized or locally advanced prostate cancer, when used alone or as adjuvant to therapy of curative intent. The risk reductions

were most pronounced in node-positive patients. These results support those of Messing and colleagues[38] and Granfors and colleagues,[39] who found that a prolongation of time to objective progression associated with early endocrine therapy in node-positive patients translated into a significant survival benefit. The EPC program is ongoing, and survival data are awaited.

See and colleagues[37] presented data showing that, irrespective of the standard therapy given, at a median follow-up of 3 years, bicalutamide significantly reduced both the risk of objective disease progression and the risk of PSA progression compared with placebo. Reductions of 37%, 37%, and 47% in the risk of objective disease progression, and of 51%, 58%, and 69% in the risk of PSA progression, were seen in the radical prostatectomy, radiotherapy, and watchful waiting groups, respectively. The investigators concluded that, irrespective of primary therapy (radical prostatectomy, radiotherapy, or watchful waiting), immediate treatment with bicalutamide, 150 mg/d, significantly reduced the risks of objective disease progression and PSA progression in patients with localized or locally advanced prostate cancer. These studies are ongoing and survival data are awaited.

The U.S. Food and Drug Administration announced the approval of the bisphosphonate zoledronic acid (Zometa, Novartis Pharmaceuticals, Chicago, IL) for use in the treatment of patients with documented bone metastases from solid tumors, including prostate cancer. Three large, international trials involving more than 3000 patients with prostate, lung, and breast cancers and other solid tumors, as well as multiple myeloma, were conducted. The number of skeletal events and the time to the first documented skeletal event were reduced by zoledronic acid therapy compared with placebo. The results of these trials are the first to show the efficacy of a bisphosphonate in treating bone complications of metastatic cancers.[40]

Bladder Cancer

Basic Research

In an experiment using cDNA expression-array technology, Kassem and colleagues[41] demonstrated that specific genes play a role in determining cellular response to radiation. To find out which patients will respond to radiotherapy and to individualize treatment, the identification of molecular predictors of radiation response would be crucial. The authors investigated the differential expression profile of stress-related and DNA repair genes in a radioresistant bladder carcinoma cell line (MGH-U1) and its radiosensitive subclone (S40b) using the Atlas Select™ Human Tumor Array (BD Biosciences Cloutech, Palo Alto, CA), a cDNA array tumor marker, to identify genes that predict radiation response.

Sangar and associates[42] investigated the radiosensitizing properties of gemcitabine in bladder tumor cell lines of differing radiosensitivity and their relation to p53 functional status. They found that the radiosensitization appeared to be p53-independent and had different sensitizing effects on different cell lines.

Immunomodulatory gene therapy has proved to be successful in experimental animal models of bladder tumor and other cancers. Brandau and coworkers[43] hypothesized that the transduction of tumor cells with the gene for CD154 could result in activation of immature dendritic cells (DCs) as the starting signal for an effective antitumor response. They tested this hypothesis using both bladder cancer cell lines and tumor tissue from patients with renal cancer. They concluded that using adenoviral transduction with the CD154 gene changed the phenotype of urologic cancers and enabled these cancer cells to activate autologous and allogeneic dendritic cells.

Irrespective of primary therapy (radical prostatectomy, radiotherapy, or watchful waiting), immediate treatment with bicalutamide, 150 mg/d, significantly reduced the risks of objective disease progression and PSA progression in patients with localized or locally advanced prostate cancer.

Mycobacterial cell-wall complex (MCC) is a cell-wall composition obtained from *Mycobacterium phlei* that contains complex mycobacterial DNA. MCC induces apoptosis in human cancer cells and stimulates cytokine synthesis by monocytic cells. MCC is currently being evaluated as a potential therapy for bladder cancer. The ability of MCC to induce apoptosis and stimulate cytokine synthesis following intravesicle administration has been determined in a phase I/II study by Phillips and colleagues[44] in patients with carcinoma of the bladder (CIS) refractory to bacille Calmette-Guérin (BCG) or chemotherapy. MCC-inhibited cellular proliferation caused specific cell-cycle arrest and induced apoptosis in human bladder cancer cell lines with differing phenotypes. The chemotherapeutic (apoptosis-inducing) and immune stimulant (cytokine inducing) activities of MCC, previously identified in vitro and in animal models, has been clinically confirmed. Both bladder cancer cell

susceptibility and patient immune-response status may influence the clinical outcome of intravesical immunotherapy.

Epidemiology

Hayne and associates[45] assessed bladder cancer incidence, mortality, and survival rates in England and Wales over the last 25 years using data from the National Cancer Intelligence Centre in London. The total number of bladder cancer cases has increased by approximately 50%, from 6918 to 10,387, between 1971 and 1997. During the same period, direct age-standardized incidence increased by 8% and 34% in men and women, respectively. Direct age-standardized mortality fell by 28% in men, with no significant change in women over the same period. Five-year relative survival rates improved to reach 63% in men and 57% in women diagnosed between 1981 and 1985, with little improvement in survival in patients diagnosed between 1992 and 1994 (66% and 58% in men and women, respectively). The total increase in bladder cancer in England and Wales may be explained by the improvement in surveillance techniques. However, the incidence of bladder cancer has been rising more rapidly in women than in men, and there has been little change in female age-standardized mortality. This may be the result of an increase in the number of women smoking. Studies have shown that women who smoke are more susceptible to bladder cancer and are more likely to develop aggressive bladder tumors than men who smoke.

Diagnosis

Combined intravenous urography (IVU) and ultrasonography (US) are standard first-line investigations in patients with hematuria. McLarty and coworkers[46] reported their experience, over an 11-year period, of using either technique alone for the primary investigation of the upper urinary tract. They suggested US as the primary imaging modality in patients with hematuria; US had a 97% primary detection rate for upper-tract transitional cell carcinoma (TCC) when combined with urine cytology. It is also more sensitive than IVU in detecting other renal masses. The investigation, according to the authors, should also be conducted in patients younger than 40 years, because TCC can present in these patients.

Studies have shown that women who smoke are more susceptible to bladder cancer and are more likely to develop aggressive bladder tumors than men who smoke.

Despite the increasing demand for an acceptable urine tumor marker for bladder cancer and the numerous published studies, with partially conflicting results, on various urine bladder tumor markers (UBTMs), there is no consensus about their clinical performance. The objective of the meta-analysis of Poulakis and associates[47] was to determine the diagnostic accuracy of all commercially available UBTMs in patients with bladder cancer. The authors selected 131 studies examining more than 17,000 patients and included them in the statistical pooling. Five UBTM tests with higher accuracy were identified for microsatellite analysis. Because of the poor methodologic quality of the available studies, it is not yet possible to develop guidelines for the effective use of UBTM in the diagnosis of bladder cancer. The use of cystoscopy in the follow-up of low grade/stage tumors and/or carcinoma in situ could not be replaced by any of these markers.

Reichelt and colleagues[48] have shown that power Doppler sonography is a reliable tool for diagnosing bladder cancer in patients with painless gross hematuria. In this study, they evaluated the diagnostic potential of echo-enhanced ultrasound in detecting TCC of the bladder compared with cystoscopy prior to transurethral resection. They used contrast-enhanced power Doppler sonography to examine 45 patients with painless hematuria who had bladder tumors diagnosed by cystoscopy. Ultrasound examination showed 48 tumors in 41 patients (of a total of 56 in 45 patients seen by cystoscopy), and the tumor vascularization of 60% of these lesions was visible before the injection of an echo-enhancing agent. They concluded that power Doppler sonography is a reliable, noninvasive, and painless diagnostic approach for detecting TCC of the bladder in patients presenting with hematuria. As soon as a vascularized lesion clearly confined to the bladder wall has been detected, the patient can be prepared for transurethral resection without performing a diagnostic cystoscopy preoperatively.

Melissourgos and associates[49] evaluated the application of helical CT images as a virtual cystoscopy and diagnostic tool in the identification of urinary bladder neoplasms. Simultaneously, the accuracy of staging cases of invasive bladder carcinoma using an axial CT was investigated. In 23 patients, virtual cystoscopy revealed 26 of 29 lesions detected by conventional cystoscopy; there were no false-positive findings. Virtual cystoscopy is minimally invasive and of equal accuracy to conventional

cystoscopy in the diagnosis of bladder neoplasms larger than 0.5 cm. Virtual cystoscopy offers valuable information about the location and size of tumors, while the simultaneous evaluation of axial CT images could be of help in determining the depth of invasion, involvement of perivesical fat, and presence of enlarged lymph nodes.

Superficial Urothelial Tumors

A number of randomized, controlled trials addressing the optimal therapy for superficial bladder cancer, particularly the efficacy of BCG, have been conducted. Nogueira and colleagues,[50] representing the Club Urologico Espanol de Tratamiento Oncologico (CUETO) study group, compared the effectiveness of an intravesical, very low dose of BCG (13.5 mg) versus a low dose of BCG (27 mg) versus MMC (30 mg), in respect to recurrence rate, time to recurrence, progression rate, and toxicity. A total of 437 patients with superficial bladder tumors underwent a transurethral resection and were randomly allocated to one of the three treatment groups. After a median follow-up of 33.1 months, the recurrence rate and the time to recurrence, as well as the progression rate, were lowest in the 27-mg BCG group (P = .001). Local and systemic toxicity was significantly higher in both BCG groups than in the MMC group. There were no significant differences in adverse effects between the two BCG treatment arms.

Solsona and coworkers,[51] also from the CUETO group, investigated the impact of MMC-induction prior to BCG on toxicity, progression, and recurrence rate, compared with BCG alone. Administration of an MMC instillation 24 hours before BCG, in an attempt to improve the immunoreaction to BCG, led to an increase in disease-free survival. However, toxicity was unacceptably high. Therefore, the authors do not advise this approach to therapy in patients with high-risk superficial bladder cancer.

Taipale and colleagues[52] compared the long-term efficacy of BCG with MMC by randomly allocating 91 patients with recurring pTa-1 tumors to receive five weekly instillations of either BCG Pasteur, 75 mg, or MMC, 20–40 mg, depending on bladder volume, 2 weeks after a transurethral resection. These treatments were followed by monthly instillations for 2 years. Intravesical BCG immunotherapy resulted in a significantly greater long-term reduction in recurrence than did MMC chemotherapy after the 2-year instillation period. In patients with early recurrences, proportionally more cases in the BCG group than in the MMC group achieved sustained disease-free status during the 2-year maintenance. The greater reduction in recurrence did not translate into fewer progressions or cancer deaths.

Kaasinen and associates[53] evaluated whether alternating instillation therapy with MMC and BCG was more effective and less toxic than conventional BCG monotherapy in patients with carcinoma in situ (CIS) of the urinary bladder. Patients with bladder carcinoma in situ were randomized to receive either BCG alone or a 6-week course of MMC instillations followed by alternating instillations of MMC or BCG every month for 1 year. Of 323 patients recruited, 304 were evaluable. At an overall median follow-up of 56 months, patients who had received BCG alone had significantly less disease recurrence than those in the alternating group. Although risk of progression also seemed lower in the BCG-alone group, there was no difference in survival between the groups, and BCG monotherapy caused more local side effects than the alternating therapy did. The authors concluded that 1-year BCG monotherapy was more effective than the tested alternating therapy for reducing recurrence and compared well with the reported best regimens of substantially smaller series. It remains unclear whether instillation therapy alters the natural course of the disease.

Virtual cystoscopy is minimally invasive and of equal accuracy to conventional cystoscopy in the diagnosis of bladder neoplasms larger than 0.5 cm.

Laboratory studies have shown that electromotive drug administration (EMDA) significantly enhances MMC transport into all of the layers of the bladder wall, compared with passive diffusion (PD). The objectives of the study by Storty and associates[54] were to compare the efficacy and side effects of intravesical MMC/PD, MMC/EMDA, or BCG in 100 patients with CIS of the bladder and to assess the pharmacokinetics of MMC. Results showed that over a 3 1/2-year period an intensive course of BCG and MMC/EMDA were equally effective for the treatment of CIS bladder cancer, and both were more effective than MMC/PD. BCG caused more side effects.

To derive conclusions from previously published studies on the use of BCG in the treatment of superficial bladder cancer and to answer the question of whether this therapy delays or prevents progression to muscle invasive disease, Sylvester and colleagues[55] conducted a meta-analysis of 21 randomized clinical trials involving 4711 patients. Their results, based on a median follow-up of 2.75

years, showed that BCG reduced the odds of progression by 25% compared with the control group, and that BCG was more effective in patients with papillary tumors only (odds to progression reduced by 35%) than in those with CIS (odds to progression reduced by 23%). The follow-up in the included studies was relatively short, and overall progression rates were low (5% for patients with papillary tumors only, 14% for CIS). The meta-analysis was hampered by clinical heterogeneity among the included studies, small sample sizes, reporting of heterogeneous results, and different definitions of progression. Nevertheless, in spite of methodologic difficulties, the authors concluded that the use of intravesical BCG appears to reduce the odds of progression to invasive muscle disease in patients with both papillary tumors and CIS, even though the absolute difference in patient numbers was small.

A prospective, monocenter, randomized, parallel-group phase III trial was performed by Filbeck and associates[56] to investigate whether primary transurethral resection with ALA-induced fluorescence diagnosis allows for a more thorough transurethral resection of superficial bladder cancer compared with conventional white light. Two primary study end points were evaluated: the residual tumor rate for judging short-term benefit of fluorescence diagnosis and the time to recurrence of the tumor for evaluating its clinical relevance. The authors demonstrated that the use of 5-aminolevulinic acid-induced fluorescence endoscopy was significantly more effective than conventional white-light transurethral resection in the primary treatment of superficial bladder cancer. Of 191 patients available for follow-up analysis, the residual tumor rate was 4.5% in the fluorescence-endoscopy arm and 25.2% in the white-light arm. There was also significant improvement in recurrence-free survival in the fluorescence-endoscopy group compared with the white-light group.

Of 191 patients available for follow-up analysis, the residual tumor rate was 4.5% in the fluorescence-endoscopy arm and 25.2% in the white-light arm.

Burgues and coworkers[57] evaluated the effectiveness of single or repeated instillations of chemotherapy versus no treatment in a randomized trial involving 812 patients with superficial bladder tumors recruited over a 5-year period. Patients received one of the following: no treatment; a single dose of adriamycin 24 hours after transurethral resection; or multiple doses of either adriamycin, thiotepa, or carcinoma in situplatin, starting 15 days after transurethral resection and repeated at intervals up to 1 year. They found that, in primary tumors only, there was a significant reduction in recurrences in the patients who received repeated chemotherapy instillations compared with those who received only one dose or no treatment. Only low-grade tumors (pTaG1 and pT1G1) were responsive to either of the chemotherapy regimens.

Invasive Bladder Cancer

Leissner and colleagues[58] presented follow-up data on a series of 321 patients who had undergone pelvic lymphadenectomy as part of radical cystectomy with curative intent in two centers. In light of the lack of evidence on the therapeutic value of this procedure, they correlated the number of lymph nodes removed with the depth of invasion of the primary tumor, the presence of nodal metastases, the clinical outcome over a mean of 35.9 months, the surgeon, and the pathologist. They found that in pT2 and pT3 tumors and those without lymph node metastases, there was a significant correlation between number of lymph nodes and tumor-free survival. The authors found that the more extensive lymphadenectomy significantly improved the prognosis of patients with invasive bladder cancer and, therefore, represents a potentially curative procedure. The results indicate a need for standardized lymph node dissection.

Madersbacher and associates[59] evaluated the relationship of local failure to distant metastases in a review of 507 patients with invasive bladder cancer who underwent radical cystectomy with extensive bilateral pelvic lymph node dissection. Overall, 44 patients (36%) remained free of disease. Median recurrence-free survival was 9.7 months, and overall survival was 15.4 months. The authors concluded that long-term survival is possible in patients with lymph node metastases undergoing radical cystectomy and extensive pelvic lymph node dissection. With higher tumor stages there is a linear increase of local and distant failure in patients with pelvic lymph node metastases.

Lymphadenectomy significantly improved the prognosis of patients with invasive bladder cancer and, therefore, represents a potentially curative procedure.

Renal Cell Cancer

Basic Research

There is a growing need for new treatment strategies to overcome the chemoresistance evident in renal cell carcinoma. The purpose of the study by Lee and colleagues[60] was to examine the functional role of clusterin, an antiapoptotic gene, in chemotherapy-induced apoptosis and to evaluate whether antisense transfection targeted against clusterin enhances chemosensitivity in renal cell carcinoma. They showed that clusterin expression was increased in the acute phase of cisplatin-induced cell death and that suppression of this clusterin expression enhanced the susceptibility of apoptosis caused by cisplatin in renal cell carcinoma. These results suggest that a chemotherapeutic strategy, in association with clusterin-suppression, may be a useful modality in enhancing the effects of cytotoxic chemotherapy in renal cell carcinoma.

Presently, interleukin-2 and/or interferon-alpha are the most frequently used treatment modalities for progressive metastatic renal cell carcinoma. However, their side effects are considerable and response rates are low (6% complete response). The development of new, more specific treatment strategies is essential. With the knowledge that the G250 antigen is expressed in 80% of all tumors associated with renal cell carcinoma, but not in normal kidney tissue, Bleumer and associates[61] investigated the presence of human lymphocyte antigen (HLA)-A2.1 restricted cytotoxic T-lymphocyte (CTL) epitopes in renal cell carcinoma, outlining the rationale for a phase 1 trial of a cell/peptide vaccine for patients with advanced renal cell carcinoma. They found that the G250 peptide 254-262 induced cytotoxic T-lymphocytes that recognized target cells expressing G250 antigen. In addition, proliferation of CD4+ T-cells was induced by dendritic cells loaded with the G250 peptide of amino acid 249-268.

Diagnosis

Patard and colleagues[62] reviewed the mode of detection of surgically treated renal tumors as a prognostic factor and compared it with usual clinical and pathologic prognostic variables. They categorized 400 patients according to whether their diagnoses had been made as a result of an incidental findings, clinical symptoms, general health alteration, or symptoms of metastasis. Tumor size was smaller in the incidental group. Specific survival was significantly better for patients with a renal tumor discovered incidentally. Tumor size, stage, grade, vein and adrenal invasion, lymphatic extension, metastasis, and mode of detection (incidentally or not) are survival prognosis factors. They concluded that, because incidental discovery of renal tumors provides a supplementary benefit to patients in terms of survival, it should be considered as a prognostic factor in addition to tumor stage and grade.

Radiotherapy

The impact of post-nephrectomy radiotherapy on local recurrence and distant metastases in patients with renal cell carcinoma who were treated with nephrectomy still remains controversial. Woiski and coworkers[63] retrospectively analyzed 251 patients with advanced renal cell carcinoma, 148 patients with Robson stage B, and 103 patients with stage C. The 5-year actuarial risk of relapse was significantly lower in stage B patients who had undergone radiotherapy than in patients with nephrectomy only. There were no significant differences for stage C patients. Similarly, the 5-year distant metastases rate was lower in stage B radiotherapy-plus-nephrectomy patients compared with those having nephrectomy alone, but no advantages were observed for stage C patients.

Li Quan-Lin and colleagues concluded that, when nephron-sparing surgery is performed in renal cell carcinoma 4 cm or less, a margin of at least 5 mm (not 10 mm) of adjacent parenchyma should be excised with the tumor.

Nephron-Sparing Surgery

Li Quan-lin and colleagues[64] prospectively studied 82 kidneys resected by radical nephrectomy in which renal cell carcinoma of 4 cm or less was present (all tumors were T1). They investigated the optimal margin of normal renal parenchyma in nephron-sparing surgery (NSS). They found 31.7% without an intact pseudocapsule and 17.1% with positive cancer lesions beyond the pseudocapsule, with invasion into normal parenchyma in 9.8%, into venules in 2.4%, and satellite tumors in 4.9%. The average distance between extra-pseudocapsule cancer lesions and primary tumors was 0.9 ± 3.0 mm. They concluded that when NSS is performed in renal cell carcinoma 4 cm or less, a margin of at least 5 mm (not 10 mm) of adjacent parenchyma should be excised with the tumor. Enucleation alone was associated with a significant risk of incomplete excision and therefore liable for local recurrence.

Despite the numerous published studies comparing survival and recurrence after NSS versus radical nephrectomy (RN) for localized renal cell carcinoma, comparative data for large patient numbers regarding the impact of these operations on quality

of life (QOL) are not available. The objective of Poulakis and associates[65] was to compare the impact on QOL of RN with that of NSS for localized renal cell carcinoma. The QOL scores of 238 patients (NSS = 96, RN = 142) were analyzed for the patient group as a whole and then compared between patients who had undergone NSS and RN. The overall cancer-targeted QOL scores and recovery from the stress of cancer in patients who underwent NSS for tumors < 4 cm and who had a normal contralateral kidney were significantly superior to those who underwent NSS for tumors > 4 cm. Patients had the highest probability of being concerned about the recurrence of cancer after mandatory NSS. Regarding the factors of fatigue, sleep disturbance, and pain, NSS exhibited lower scores compared with RN. QOL correlated proportionally with NSS for tumors < 4 cm and a normal contralateral kidney.

The majority of renal cell cancer patients are overtreated with adrenalectomy as an integrated part of tumor nephrectomy.

Laparoscopic Surgery

Laparoscopic radical nephrectomy (LRN) has only recently gained wider acceptance. Initially, there was concern about achieving an appropriate oncologic resection of the tumor and about port-site recurrences from tumor-seeding. Lianos and colleagues[66] prospectively evaluated the efficacy and feasibility of using LRN for renal cell carcinoma in 25 patients. LRN was undertaken using a transperitoneal approach with three or four ports, employing the same oncologic principles as those for open radical nephrectomy. The mean operative time was 143.4 minutes, the mean hospital stay was 5.5 days, and there were no tumor recurrences. The authors concluded that LRN can be safe and effective for renal cell carcinoma, with excellent tumor control for low-grade disease, maintaining strict oncologic principles.

Klingler and associates[67] compared 38 transperitoneal LRNs with 38 open radical nephrectomies. In the laparoscopic group, the operation time was longer (mean: 187 minutes vs 159 minutes), but postoperative pain and hospital stay (5.1 vs 13.4 days) were both significantly less.

In another prospective study, Klingler and associates[68] sought to determine whether patients with a higher body mass index (BMI) would benefit most from laparoscopic procedures in respect to postoperative morbidity and pain compared with control patients. A total of 62 laparoscopic kidney procedures were performed at the University of Vienna. Twenty-five were radical nephrectomies with adrenalectomy, and 12 were without adrenalectomy. Six nephrectomies were for benign disease, and 19 were nephron-sparing partial nephrectomies. In all patients, the Visual Analogue Symptom Score was evaluated. The authors concluded that patients with a higher BMI have less postoperative pain and seem to benefit more from laparoscopy compared with thinner patients. According to these findings, we suggest that patients with a BMI < 28 kg/cm^2 receive intraoperative paraganglionic blockage to decrease perioperative morbidity.

According to these findings, we suggest that patients with a BMI < 28 kg/cm^2 receive intraoperative paraganglionic blockage to decrease perioperative morbidity.

Routine Adrenalectomy for Renal Cell Carcinoma?

In the absence of clinically overt metastatic disease, tumorous lesions within the adrenal gland are found in only 2%–10% of cases; thus, the majority of renal cell cancer patients are overtreated with adrenalectomy as an integrated part of tumor nephrectomy. Debate is ongoing about the need for routine removal of the ipsilateral adrenal gland as part of perifascial nephrectomy. Kuczck and colleagues[69] reviewed the medical records of 847 patients undergoing adrenalectomy in combination with nephrectomy, regardless of local extension of the primary tumor or clinical stage at first diagnosis, in order to determine the reliability of currently available imaging modalities for predicting adrenal gland metastases. None of the characteristics of the patients, or the tumors that were evaluated, reliably predicted the likelihood for the presence of adrenal metastases in patients without evidence of disseminated metastatic spread. The frequency of metachronous metastases within the contralateral kidney (2%–4%) is significantly higher than the risk of a preoperatively undetected, isolated, adrenal metastasis, when currently available imaging modalities are applied. Therefore, routine adrenalectomy should not be recommended in cases of preoperative normal radiologic examinations.

Prognosis

With the earlier detection of renal

cell carcinoma and the development of more specific immunotherapy, the prognosis of patients with renal cell carcinoma is improving. The task of further individualizing these treatment modalities increases the importance of identifying adequate prognostic subgroups. Therefore, the University of California at Los Angeles Integrated Staging System (UISS) was recently proposed.[70] The UISS includes the TNM staging system, the Führman pathological grading system, and the Eastern Cooperative Oncology Group (ECOG) performance status. Mulders and associates[71] evaluated the use of this staging system using the records of 207 patients in their renal cell carcinoma database. Employing the UISS system, they divided the patients in the database into five subgroups. The 2-year and 5-year survival rates of the different groups were estimated, each with a different survival curve, and the authors proposed this system for future trial design and treatment decisions for patients with renal cell carcinoma.

To better understand the function of the remaining kidney following nephrectomy, Kastin and colleagues[72] evaluated remaining kidney function using dimercaptosuccinic acid (succimer) (DMSA) scan and serum creatinine levels pre- and post-operative in 40 patients. Following surgery, the DMSA scan of the remaining kidney demonstrated a significant uptake elevation (3.845%), probably resulting from a compensatory mechanism. A preoperative absolute uptake of < 11% in the remaining kidney was found to be a risk factor for developing chronic renal failure.
[Christian Seitz, MD, Mesut Remzi, MD, Bob Djavan, MD, PhD]

Treatment of Benign Prostatic Hyperplasia

For over 10 years, clinical and basic research regarding medical therapy for BPH has occupied the center stage in national and international urological meetings. In that time, four α-adrenergic receptor blockers have been tested in large-scale safety and efficacy trials. All have been found superior to placebo and are currently approved for use in most countries. These drugs are the titratable α-receptor blockers terazosin and doxazosin, and tamsulosin and alfuzosin, which require no dose titration. At this year's meeting, a new compound was introduced: dutasteride, a dual inhibitor of both isoenzymes of the 5-α-reductase enzyme.

A preoperative absolute uptake of < 11% in the remaining kidney was found to be a risk factor for developing chronic renal failure.

Alfuzosin

Alfuzosin was initially made available in a 2.5-mg tid dosage and, subsequently, in a 5-mg bid dosage. It has now been introduced in Europe in a 10-mg, once-a-day geometrics formulation requiring no dose titration. Appropriate phase III trials of the formulation have also been conducted in the United States (ALFUS) and the dossier has been submitted by Sanofi-Synthélabo to the U.S. Food and Drug Administration, with a likely approval date of 2003.

The safety and efficacy of alfuzosin, 10 mg, was presented at the EAU as a pooled analysis of all three randomized, placebo-controlled, double-blind studies, enrolling a total of 693 patients.[73] Alfuzosin, 10 mg/d, was found to be superior to placebo in terms of symptom score improvement (−6 vs −4.2 points; $P < .001$) and peak urinary flow rate improvement (+2.3 vs +1.1 mL/s; $P < .001$). In general, alfuzosin, 10 mg, was well tolerated, with cardiovascular-related adverse events occurring in 6.1% of alfuzosin and 2.9% of placebo-treated patients. The incidence of cardiovascular adverse events was not affected by age, hypertension status, or antihypertensive drug intake.

Tamsulosin

Several abstracts were presented detailing studies of tamsulosin. Michael O'Leary of Brigham and Women's Hospital, Boston, presented data from an open-label, 4-year extension, multicenter trial with tamsulosin, 0.4 mg, in what was originally a total of 609 eligible patients.[74] Of these 609, 419 patients completed 5-year follow-up, and 109 patients completed 6 years of follow-up. At the 5-year time point, there was significant improvement from baseline in symptom score and peak urinary flow rate, with an acceptable safety profile.

Tamsulosin for Acute Urinary Retention

Malcolm and colleagues[75] presented results from a multicenter, randomized, double-blind, placebo-controlled clinical trial in elderly men presenting to the hospital with acute urinary retention. Patients were randomized to receive either tamsulosin, 0.4 mg, or placebo for 3–7 days, after which a trial without catheterization was carried out. A total of 149 patients were randomized, of whom 71 received tamsulosin, 70 received placebo, and 8 dropped out. A substantial number of patients failed a trial without catheterization and required recatheterization. Successful voiding occurred in more patients randomized to tamsulosin than in the placebo group, and significantly fewer

patients receiving tamsulosin required re-catheterization compared with placebo (49.3% vs 70%; P = .011). This study adds to the mounting evidence that at least precipitated episodes of acute urinary retention can be successfully treated with several days of therapy with a fast-acting α-blocker, followed by a trial without catheter. Considering that in clinical practice more than half of all episodes of acute urinary retention are precipitated (by unrelated surgery, cold medications, anesthesia for unrelated reasons, etc), α-adrenergic receptor-blocker therapy is a useful adjunct in the management of such patients and will likely reduce the number of patients subjected, perhaps too hastily, to surgery.

Tamsulosin Versus Saw Palmetto Berry

In a double-blind, randomized, international trial performed in 11 European countries, tamsulosin, 0.4 mg, was compared with a standard dose of the phytotherapeutic agent permixon, which is a pure extract of the saw palmetto berry (*Serenoa repens*).[76] A total of 811 patients with a symptom score of >10 points and a peak flow rate of 5–15 mL/s were recruited, of whom 704 were randomized to tamsulosin (n = 354) or permixon (n = 350). After 12 months of treatment, the symptom score for the tamsulosin group decreased 4.4 points; the permixon group experienced an identical symptom improvement. Peak urinary flow rate was improved by 1.8 mL/s and 1.9 mL/s in the tamsulosin and permixon groups, respectively, and all other parameters were identical between the two treatment groups. It is most intriguing that this study shows equivalent efficacy between the saw palmetto berry extract and the standard dose of 0.4 mg tamsulosin. Unfortunately, this study did not have a placebo-control group.

Significantly fewer patients receiving tamsulosin required re-catheterization, compared with placebo.

It is hoped that the NIDDK consortium will be able to address some of the important scientific and clinical issues surrounding the use of phytotherapeutic agents.

The National Institute of Diabetes & Digestive & Kidney Diseases recently released a request for application, with the intent of establishing a consortium of investigators to conduct several multicenter clinical trials in the area of phytotherapeutic agents for the treatment of LUTS and clinical BPH. It is hoped that the consortium, which will be convened later this year, will address some of the important scientific and clinical issues surrounding the use of phytotherapeutic agents and clarify their relative position in the treatment armamentarium for LUTS and BPH.

Hormonal Agents for BPH

Finasteride

The only hormonal agent useful in the treatment of BPH thus far is the 5-α-reductase inhibitor finasteride (Proscar,® Merck and Co., Inc., Whitehouse Station, NJ), which has been extensively tested in pivotal phase III and subsequent clinical trials. Most notably, the Proscar Long-Term Efficacy and Safety Study (PLESS) provided a wealth of information regarding the usefulness of finasteride in men with enlarged prostates and higher serum PSA levels. The 4-year PLESS study was followed by an open-label extension, during which a total of 16,777 patients received finasteride for an additional 2 years. This is a remarkably high percentage of the 18,883 patients who completed the original 4-year study. Data presented demonstrated that, in the subsequent 2 years of the study, the patients who switched from placebo to finasteride experienced a rapid and sustained reduction in the incidence rates of acute urinary retention and/or BPH-related surgery.[77]

The annual rate of acute urinary retention in the finasteride-treated patients in the first 4 years of the study ranged from 1.0% to 2.1%, versus 3.0% to 4.4% in the placebo-treated patients. During years 5 and 6 of the open-label extension, however, the yearly incidence rate in the original finasteride group was 0.7% and 1.4%, respectively, whereas in the previously placebo-treated patients, the rate dropped to 1.5% and 1.6%, respectively. These data demonstrate that the beneficial effects in terms of the incidence rate of acute urinary retention and/or BPH-related surgery takes place rather quickly and is independent of the time at which the diagnosis is established and/or therapy is initiated.

Dutasteride

It is well known that finasteride, the first 5-α-reductase inhibitor clinically used, is a selective inhibitor of the 5-α-type II isoenzyme. In fact, it is an incomplete inhibitor of the isoenzyme, reducing circulating levels of

serum dihydrotestosterone (DHT) by slightly more than 70% on average. In the past decade, several 5α-reductase inhibitors have been tested in phase I and II trials, but only one has been explored in a phase III program. Dutasteride is a dual inhibitor of both isoenzymes of the 5α enzyme and, because of its near-complete inhibition of both isoenzymes, it reduces serum DHT levels by more than 90%.

Although it is clear that the inhibition of the conversion of testosterone to DHT and the subsequent reduction of intraprostatic DHT is the main mechanism of action of finasteride, it remains to be seen whether the more complete reduction of circulating DHT in the serum will translate into greater efficacy of a dual inhibitor such as dutasteride. GlaxoSmithKline, the manufacturer of dutasteride, launched an ambitious phase III trial program, which consisted of three parallel-conducted, randomized, placebo-controlled studies, each of 2 years duration. A total of 4325 patients were randomized, of whom 2951 completed the 24-month study.[78,79] In addition to the typical inclusion and exclusion criteria, patients had to have a TRUS-measured prostate volume of > 30 mL, as well as a serum PSA of ≥ 1.5 ng/mL. These criteria were based on prior experience with finasteride, which demonstrated greater efficacy in patients with larger glands and higher serum PSA levels (whereas in the PLESS trial, finasteride proved to be nearly equivalent to placebo in men with a PSA < 1.3 ng/mL).

The primary outcome parameter, the International Prostate Symptom Score, was reduced by 4.6 points, versus a 2.3-point reduction with placebo ($P < .001$), at the end of 24 months. Peak flow rate improved as early as 1 month in one of the three studies, and by 3 months in all studies, and at the end of 24 months the improvement was 2.0 mL/sec and 0.9 mL/sec in the dutasteride and placebo groups, respectively ($P < .001$). In addition, BPH-specific health status was significantly improved, as were other humanistic assessments. Both total prostate volume and transition zone volume were measured by TRUS at baseline, 3, 6, 12, and 24 months. In one study, prostate volume was additionally measured at 1 month. With dutasteride therapy, the reduc-

Main Points

- Prostate specific-antigen (PSA) studies have shown that free PSA (fPSA) and total PSA (tPSA) levels in archival ethylenediaminetetraacetic acid plasma, stored for 25 years at –20° C, are not significantly different from those in freshly collected samples; and f/t PSA ratios may detect organ-confined prostate cancer when tPSA is between 1.1 ng/mL and 4.0 ng/mL.
- Studies have shown that complex PSA (cPSA) indices improve cancer detection in patients with PSA levels from 4.0 ng/mL to 10.0 ng/mL, and cPSA performed better diagnostically and improved specificity over tPSA; c/t PSA and transition zone volume combined were highly predictive of cancer on a repeat biopsy.
- A study found that the use of waterjet dissection during nerve-sparing radical prostatectomy was safe and easy to learn, reduced blood loss by 36%, decreased operation time by 20%, and improved outcome with respect to potency.
- Robotically-assisted laparoscopy may expand the range of laparoscopic operative approaches. Nomograms have been shown in the United States to be valid in calibrating and predicting radical prostatectomy outcomes.
- Regarding bladder cancer, one study found that radiosensitization appeared to be p53-independent and had different sensitizing effects on different cell lines. Another study concluded that adenoviral transduction with the CD154 gene changed the phenotype of urologic cancers, enabling them to activate dendritic cells for antitumor response.
- Doppler sonography is reliable for diagnosing transitional cell carcinoma of the bladder in patients with hematuria. In addition, virtual cystoscopy is minimally invasive and as accurate as conventional cystoscopy in diagnosing bladder neoplasms larger than 0.5 cm.
- In a pooled analysis of three randomized, placebo-controlled, double-blind studies, alfuzosin, 10 mg/d, was superior to placebo in terms of symptom score improvement and peak urinary flow rate improvement.
- Data from the 2-year extension of the Proscar Long-Term Efficacy and Safety Study (PLESS), in which a total of 16,777 patients received finasteride, demonstrated that patients who had been receiving placebo but were switched to finasteride experienced a rapid and sustained reduction in the incidence rates of acute urinary retention and/or benign prostatic hyperplasia (BPH)-related surgery.
- Results from phase III studies of dutasteride, a 5-α-reductase inhibitor, showed remarkable similarities to those for finasteride in PLESS: patients with larger prostates and higher PSA levels respond more favorably to dutasteride than to placebo, and the risk reduction in terms of acute urinary retention and BPH-related surgical interventions is nearly identical between dutasteride and finasteride.

tion of total prostate volume was 8.6% at 1 month; transition zone volume decreased 6.9%. In the entire cohort, the percent reduction of total prostate volume was 25.9% at 12 months and 28.5% at 24 months; the transition zone volume was reduced by 23% and 26.8% at these two time points, respectively. Circulating DHT levels decreased by 93.4% at 24 months, and more than 90% of patients achieved a decrease of > 90% at 12 months. The mean increase in serum testosterone was comparable to that observed with finasteride. There were 90 episodes of acute urinary retention in the placebo-treated patients, for an incidence of 4.2%, versus 39 episodes in the dutasteride group, for an incidence of 1.8%. This risk reduction of 57% ($P < .001$) is identical to the risk reduction of acute urinary retention observed in the first 4 years of the PLESS trial. Surgical interventions for LUTS and BPH took place in 89 placebo-treated patients versus 47 dutasteride-treated patients, for an incidence of 4.1% versus 2.2% and a risk reduction of 48% ($P < .001$). Total serum PSA was measured in all patients at baseline, 12, and 24 months, and fPSA was measured in a subset. The mean reduction in serum PSA was 52.4%, and the mean reduction in fPSA was 55.5%. The free-to-total ratio did not change significantly; thus, it can be concluded that the utility of serum PSA is maintained by multiplying the tPSA by 2 after exposure to dutasteride and utilizing the f/t PSA ratio in the same manner as always.

The clinical similarities between the dutasteride phase III studies and the PLESS studies are striking. Improvement in symptom score and urinary flow rate occurred at similar time points and are of a similar magnitude. As with finasteride in the PLESS trial, patients with larger prostates and higher PSA levels respond more favorably to dutasteride, and the risk reduction in terms of acute urinary retention and BPH-related surgical interventions is nearly identical.

Surgical interventions for LUTS and BPH took place in 89 placebo-treated patients, versus 47 dutasteride-treated patients.

Findings of this nature should be comforting to physicians and patients alike. In the past, the 5-α-reductase inhibitor class had only a single agent, namely finasteride. Dutasteride, the second entry into this class, confirms the data obtained with finasteride, specifically the careful and stratified analyses done on the PLESS database. 5-α-Reductase inhibitors will likely find a permanent place in the medical therapeutic armamentarium for men whose LUTS are clearly due to BPH with significant prostatic enlargement and likely stromoglandular hyperplasia. These men can easily be identified clinically by a serum PSA level > 1.5 ng/mL. It is in precisely this cohort of patients at risk for progression that the 5-α-reductase inhibitors exhibit their greatest efficacy, and the risk reduction for acute urinary retention and surgery is the greatest. In these men, use of 5-α-reductase inhibitors represents the greatest opportunity for cost-effective management. ■

[Claus G. Roehrborn, MD, FACS]

[Note: Dr. Roehrborn has served as an investigator for GlaxoSmithKline and for Sanofi-Synthélabo.]

References

1. Ulmert D, Becker C, Björk T, et al. Excellent stability of free and total PSA in EDTA-plasma after storage at -20˚C for 25 years [abstract]. *Eur Urol.* 2002;1(suppl):97.
2. Djavan B, Zlotta A, Ravery V, et al. Prospective multicenter European study of complex PSA, CPSA, CPSAD, CPSA-TZ , C/total PSA ratio, C/free PSA ratio, F/T PSA, PSAD and PSA-TZ for early prostate cancer detection in men with PSA levels B [abstract]. *Eur Urol.* 2002;1(suppl):98.
3. Rowe E, Patel A, Walker M, et al. The utility of the free/total PSA ratio in prostate cancer detection in younger men aged 50-65 years with a 'normal' total PSA [abstract]. *Eur Urol.* 2002;1(suppl):96.
4. Bartsch G, Cheli CD, Babaian R, et al. Results of a multicenter prospective evaluation of complexed PSA [abstract]. *Eur Urol.* 2002;1(suppl):99.
5. Volgger H, Horninger W, Steiner H, et al. Consideration of low PSA levels to optimise the detection of curable prostate cancers: results of the Tyrol PSA screening project [abstract]. *Eur Urol.* 2002;1(suppl):98.
6. Horninger W, Rogatsch H, Volgger H, et al. Low-volume prostate cancers with low PSA levels are multifocal tumours [abstract]. *Eur Urol.* 2002;1(suppl):97.
7. Tuukka M, Auvinen A, Tammela T, et al. Characteristics of prostate cancer in the Finnish screening trial with prostate-specific antigen (PSA) [abstract]. *Eur Urol.* 2002;1(suppl):76.
8. Irani J, Ravery V, Pariente J, et al. Nonsteroidal anti-inflammatory agents and finasteride and risk for prostate cancer [abstract]. *Eur Urol.* 2002;1(suppl):76.
9. Valeri A, Cormier L, Cancel-Tassin G, et al. PSA levels in unaffected first degree relatives of prostate cancer patients are higher than in men without family history of the disease [abstract]. *Eur Urol.* 2002;1(suppl):75.
10. Luboldt HJ, Fornara P, Jocham D, et al. Early detection of prostate cancer in Germany: development of an evidence based guideline [abstract]. *Eur Urol.* 2002;1(suppl):76.
11. Leon S, McLeod D, Amling C, et al. Epidemiology of prostate cancer, its treatment and outcome: introduction of the department of defense center for prostate disease research (DOD-CPDR) multicenter prostate cancer database with 307, 931 records on 13,878 men [abstract]. *Eur Urol.* 2002;1(suppl):74.
12. Massood J, Shah N, Lane T, et al. Entonox inhalation and tolerance of trans-rectal ultrasound guided (TRUS) prostate biopsy- a double blind randomized controlled study [abstract]. *Eur Urol.* 2002;1(suppl):118.
13. Nambirajan T, Woolsey S, Mahendra V, et al. Prospective, randomized, placebo controlled trial of periprostatic local anaesthetic in transrectal prostate biopsy [abstract]. *Eur Urol.* 2002;1(suppl):117.
14. Otite U, Stewart E, Gordon S, et al. Evaluation of 5% lignocaine ointment on patient tolerance to transrectal ultrasound (TRUS) guided prostatic biopsy [abstract]. *Eur Urol.* 2002;1(suppl):118.
15. Remzi M, Djavan B, Tinzl M, et al. How to improve our decision making to perform repeat biopsies: the impact of total and transition zone volume in patients with intermediate and low PSA levels [abstract]. *Eur Urol.* 2002;1(suppl):167.
16. Djavan B, Tinzl M, Zlotta A, et al. Complex PSA and complex PSA indices in combination with artificial neural networks to predict the outcome of repeat prostate biopsies: results of the European prostate cancer detection study

[abstract]. *Eur Urol.* 2002;1(suppl):119.
17. Di Stasi SM, Fortuna G, Storti L, et al. Radical retropubic prostatectomy versus external beam radiotherapy for clinically localised prostate cancer: preliminary results of a controlled randomised trial [abstract]. *Eur Urol.* 2002;1(suppl):45.
18. Hammerer P, Schwarz R, Krüll A, et al. Results of conformal radiotherapy for local recurrences after radical prostatectomy (RP) [abstract]. *Eur Urol.* 2002;1(suppl):45.
19. Van der Hoeven J, Bevers R, van Moorselaar J, et al. A prospective study of erectile function following transperineal I-125 seed implantation for localized prostate cancer [abstract]. *Eur Urol.* 2002;1(suppl):46.
20. Stone NG, Stock R. Safety and efficacy of prostate brachytherapy in patients with prior TURP [abstract]. *Eur Urol.* 2002;1(suppl):46.
21. Losa A, Nava L, Maga T, et al. Quality of life and sexual function after palladium 103 prostate brachytherapy [abstract]. *Eur Urol.* 2002;1(suppl):46.
22. Hofer C, Poth C, Hartung R, et al. Does not performing pelvic lymph adenectomy in patients undergoing radical prostatectomy result in a reduced morbidity? [abstract]. *Eur Urol.* 2002;1(suppl):69.
23. Palisaar J, Graefen M, Hammerer P, et al. Assessment of clinical and pathologic characteristics predisposing to biochemical disease recurrence following radical prostatectomy (RP) in men with pathologically organ confined prostate cancer (PCA) [abstract]. *Eur Urol.* 2002;1(suppl):70.
24. Fernandez S, Noldus J, Conrad S, et al. Experience with water-jet dissection in nerve sparing radical prostatectomy (NSRRP) [abstract]. *Eur Urol.* 2002;1(suppl):3.
25. Guillonneau B, Gerard C, Cathelineau X, et al. Mid-term oncological follow-up of laparoscopic radical prostatectomy: mono-institutional experience based on 730 consecutive patients [abstract]. *Eur Urol.* 2002;1(suppl):4.
26. Guillonneau B, Fromont G, Validire P, et al. Pathological results of neurovascular bundle preservation during laparoscopic radical prostatectomy [abstract]. *Eur Urol.* 2002;1(suppl):70.
27. Rassweiler J, Gaitonde K, Paz A, et al. Laparoscopic radical prostatectomy with the Heilbronn Techniquethe learning curve and complications during the first 300 cases [abstract]. *Eur Urol.* 2002;1(suppl):4.
28. Roumeguere T, Bollens R, Van den Bossche M, et al. Functional evaluation at one year after extraperitoneal laparoscopic radical prostatectomy [abstract]. *Eur Urol.* 2002;1(suppl):4.
29. Wolfram M, Jones J, Hagel C, et al. Robotically-assisted laparoscopic radical prostatectomy: the Frankfurt technique [abstract]. *Eur Urol.* 2002;1(suppl):4.
30. Boreley N, Sriprasad S, Thompson P, et al. Laparoscop lymph node staging is more sensitive than MRI in high risk prostate cancer [abstract]. *Eur Urol.* 2002;1(suppl):56.
31. Cadeddu JA, Elashry OM, Snyder O, et al. Effect of laparoscopic pelvic lymph node dissection on the natural history of D1 (T1-3, N1-3, M0) prostate cancer. *Urology.* 1997;50:391–394.
32. Ross PL, Scardino PT, Kattan MW et al. A catalog of prostate cancer nomograms. *J Urol.* 2001;65(suppl 1):1562–1568.
33. D'Amico M, Whittington R, Malkowicz SB, et al. Pretreatment nomogram for prostate-specific antigen recurrence after radical prostatectomy or external-beam radiation therapy for clinically localized prostate cancer. *J Clin Oncol.* 1999;17:168–172.
34. Graefen M, Karakiewicz P, Cagiannos I, et al. A comparison of two preoperative nomograms predicting recurrence following radical prostatectomy [abstract]. *Eur Urol.* 2002;1(suppl):66.
35. Steineck G, Åstrom K, Eriksson E, et al. Castration and osteoporis related fractures in a 30-year follow-up [abstract]. *Eur Urol.* 2002;1(suppl):134.
36. Iversen P, Wirth M, See W, et al. Is the efficacy of hormonal therapy affected by lymph node status? New data from the bicalutamide EPC programme [abstract]. *Eur Urol.* 2002;1(suppl):134.
37. See W, Wirth M, McLeod D, et al. Immediate treatment with bicalutamide reduces the risk of disease progression in early non-metastatic prostate cancer irrespective of primary therapy [abstract]. *Eur Urol.* 2002;1(suppl):134.
38. Messing EM, Manola J, Sarosdy M, et al. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. *N Engl J Med.* 1999;341:1781–1788.
39. Granfors T, Modig H, Damber J, et al. Combined orchiectomy and external radiotherapy versus radiotherapy alone for nonmetastatic prostate cancer with or without pelvic lymph node involvement: a prospective randomized study. *J Urol.* 1998;159:2030–2034.
40. Novartis Pharmaceuticals Corporation. Zometa approved [press release]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; February 22, 2002.
41. Kassem H, Sangar V, Cowan R, et al. Differential gene expression of bladder cancer cell lines with different radiosensitivity using Atlas CDNA arrays [abstract]. *Eur Urol.* 2002;1(suppl):19.
42. Sangar V, Roberts S, Cowan R, et al. Differential radiosensitisation of bladder cancer cell lines by gemcitabine and its relationship to P53 status and cell cycle perturbations [abstract]. *Eur Urol.* 2002;1(suppl):42.
43. Brandau S, Loskog A, Tötterman T, et al. Mechanisms of immune-gene-therapy: activation of dendritic cells by AD-CD154 transduced tumour cells [abstract]. *Eur Urol.* 2002;1(suppl):43.
44. Phillips N, Filion M, Filion B, et al. Apoptosis-inducing and immune stimulant activity of mycobacterial cell wall complex in patients with treatment-refractory cis [abstract]. *Eur Urol.* 2002;1(suppl):43.
45. Dicken H, Arya M, Hamid R, et al. A study of the trends in bladder cancer in England and Wales over 25 years [abstract]. *Eur Urol.* 2002;1(suppl):77.
46. McLarty E, Kazemi A, Gill K, et al. Upper tract imaging in patients presenting with haematuria: the role of ultrasound [abstract]. *Eur Urol.* 2002;1(suppl):47.
47. Poulakis V, Witzsch U, deVries R, et al. Accuracy of commercially available urine bladder tumour markers in the diagnosis of bladder cancer: a meta-analysis with summary roc curve analysis [abstract]. *Eur Urol.* 2002;1(suppl):48.
48. Reichelt O, Wunderlich H, Schubert J, et al. Contrast-enhanced power Doppler sonography versus cystoscopy: what is more accurate in diagnosing transitional cell carcinoma of the urinary bladder? [abstract]. *Eur Urol.* 2002;1(suppl):49.
49. Melissourgos N, Davilas I, Liapis D, et al. Comparison of virtual cystoscopy and conventional cystoscopy findings in patients with bladder cancer [abstract]. *Eur Urol.* 2002;1(suppl):49.
50. Nogueira M, Solsana E, Unda M, et al. A multicentre and randomized prospective study comparing three intravesical therapies, two with bacillus calmetteguerin immunotherapy and one with mitomycin-C chemotherapy in medium and low risk superficial bladder tumours [abstract]. *Eur Urol.* 2002;1(suppl):101.
51. Solsona E, Gonzalez M, Fernandez JM, et al. Random trial comparing intravesical chemoinduction with MMC to BCG versus intravesical BCG, in patients with intermediate-high risk superficial bladder cancer. Efficacy evaulation of CUETO trial N93008 [abstract]. *Eur Urol.* 2002;1(suppl):101.
52. Taipale Kaasinen E, Juusela H, et al. The effect of BCG and mitomycin C instillation treatment in recurrent superficial bladder carcinoma. 15-year follow-up of a randomized prospective Finn bladder study [abstract]. *Eur Urol.* 2002;1(suppl):101.
53. Kaasinen E, Wijkström H, Malmström P, et al. Alternating mitomycin C and BCG instillations versus BCG alone in the treatment of carcinoma in situ of the urinary bladder. A Nordic study [abstract]. *Eur Urol.* 2002;1(suppl):101.
54. Storti L, Giurioli A, Zampa G, et al. Intravesical bacillus Calmette-guerin versus passive diffusion and electromotive administration of mitomycin C in patients with carcinoma in situ of the bladder: a randomized crossover study [abstract]. *Eur Urol.* 2002;1(suppl):122.
55. Sylvester R. Symposium: BCG in superficial bladder cancer: facts and fiction. Presented at: XVIIth Congress of the European Association of Urology; February 23–26, 2002; Birmingham, UK.
56. Filbeck T, Pichlmeier U, Knuechel R, et al. 5-aminolevulinic acid induced fluorescence endoscopy decreases recurrence rate of superficial bladder carcinoma [abstract]. *Eur Urol.* 2002;1(suppl):121.
57. Burgues JP, Pontones JL, Alapont JM, et al. Intravesical chemotherapy for superficial bladder tumours: 5-year follow-up of a randomized trial comparing early single dose versus delayed long-term chemotherapy versus no treatment [abstract]. *Eur Urol.* 2002;1(suppl):122.
58. Leissner J, Hohenfellner R, Wolf H, et al. Significance of pelvic lymphadenectomy for the prognosis after radical cystectomy [abstract]. *Eur Urol.* 2002;1(suppl):137.
59. Madersbacher S, Thalmann G, Markwalder R, et al. The relationship of local to distant failure in pelvic lymph node positive patients after radical cystectomy [abstract]. *Eur Urol.* 2002;1(suppl):137.
60. Lee C, Kwak C, Park MS, et al. The effect of clusterin suppression in combination with cisplatin on renal cancer cell line [abstract]. *Eur Urol.* 2002;1(suppl):142.
61. Bleumer I, Tiemessen D, Oosterwijk-Wakka J, et al. Immunogenecity of G250 peptides: rationale for a dendritic cell/peptide vaccine trial in patients with advanced renal cell carcinoma [abstract]. *Eur Urol.* 2002;1(suppl):142.
62. Patard JJ, Rodriguez A, Lhorfi H, et al. Prognosis significance of the mode of detection in 400 renal tumours [abstract]. *Eur Urol.* 2002;1(suppl):173.
63. Woiski Z, Zarzycka M, Windorbska W, et al. Probability of late recurrence and distant metastases after nephrectomy and radiotherapy in renal cell carcinoma [abstract]. *Eur Urol.*

2002;1(suppl):174.
64. Quan-lin L, Hong-wei G, Qiu-ping Z, et al. Optimal margins in nephron-sparing surgery for renal cell carcinoma [abstract]. *Eur Urol*. 2002;1(suppl):26.
65. Poulakis V, Witzsch U, Lippert C, et al. Quality of life after surgery for renal cell carcinoma: comparison between radical nephrectomy and nephron-sparing surgery [abstract]. *Eur Urol*. 2002;1(suppl):27.
66. Lianos E, Wilson I, Esposito M, et al. Laparoscopic radical nephrectomy for renal cell carcinoma: the Edinburgh experience [abstract]. *Eur Urol*. 2002;1(suppl):28.
67. Klingler C, Remzi M, Schmidbauer J, et al. Comparison of laparoscopic transperitoneal and open radical nephrectomy for treatment of localized renal cell cancer [abstract]. *Eur Urol*. 2002;1(suppl):28.
68. Klingler C, Remzi M, Schmidbauer J, et al. Patients with a higher body mass index have less pain after laparoscopic kidney surgery [abstract]. *Eur Urol*. 2002;1(suppl):5.
69. Kuczck M, Munch T, Machtens S, et al. The need for routine adrenalectomy during the surgical treatment of renal cell cancer– the Hanover experience[abstract]. *Eur Urol*. 2002;1(suppl):72.
70. Zisman A, Pantuck AJ, Dorey F, et al. Improved prognostication of renal cell carcinoma using an integrated staging system. *J Clin Oncol*. 2001;5:1649–1657.
71. Mulders P, Debruyne F, deMulder P, et al. Updated prognostication of renal cell carcinoma patients [abstract]. *Eur Urol*. 2002;1(suppl):173.
72. Kastin A, Mullerad M, Amiel G, et al. Utilising quantitative TC 99M-DMSA renal scintigraphy to predict postoperative renal failure in patients undergoing radical nephrectomy [abstract]. *Eur Urol*. 2002;1(suppl):174.
73. Roehrborn C, Van Kerrebroeck P, Nordling J. Safety and efficacy of alfuzosin 10 mg once daily: a pooled analysis of three double-blind placebo-controlled studies [abstract]. *Eur Urol*. 2002;1(suppl):106.
74. O'Leary M. Tamsulosin demonstrates long-term efficacy on multiple clinical and quality-of-life scoring systems [abstract]. *Eur Urol*. 2002;1(suppl):106.
75. Lucas M, Stephenson T, Nargund V. Tamsulosin in the management of patients in acute urinary retention due to benign prostatic hyperplasia [abstract]. *Eur Urol Suppl*. 2002;1(suppl):106.
76. Debruyne F, on behalf of the PERMAL Study Group. Comparison of a phytotherapeutic agent (permixon) with an alpha blocker (tamsulosin) in the treatment of benign prostatic hyperplasia: a 1-year randomised international study [abstract]. *Eur Urol*. 2002;1(suppl):108.
77. Roehrborn C. Rapid reduction in risk of AUR and/or surgery with finasteride in men with benign prostatic hyperplasia [abstract]. *Eur Urol*. 2002;1(suppl):107.
78. Roehrborn C, Andriole G, Boyle P, Hofner K. Effect of the dual 5 alpha-reductase inhibitor dutasteride on endocrine parameters and prostate volume [abstract]. *Eur Urol*. 2002;1(suppl):107.
79. Boyle P, Roehrborn C, Andriole G, Nickel JC, et al. The impact of dutasteride, a novel 5-α reductase inhibitor, on the hallmarks of BPH. Progression and outcomes. *Eur Urol*. [abstract]. 2002;1(suppl):107.