

Oncological Update: New Findings in Bladder and Prostate Cancer

*Highlights From the 25th Anniversary Congress of the European Association of Urology,
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The impact of the volcanic ash cloud generated out of Iceland complicated the journey to the 25th Anniversary Annual Congress of the European Association of Urology in Barcelona, April 16-20, 2010, for many of the congress participants. Nevertheless, the force majeure circumstances did not cause any major changes in the congress program and the vast majority of the 1104 abstracts and 50 videos were finally presented.

Regarding urothelial carcinoma of the bladder, a large array of posters and videos were presented. Major

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topics included basic research, prognostic factors, and outcome, as well as management of muscle- and non-muscle-invasive bladder cancer. Moreover, important new findings in prostate cancer (PCa) were presented on basic research, diagnosis, prostate biopsy, radical prostatectomy, and postoperative complications.

Bladder Cancer

Basic Research

Arentsen and colleagues¹ presented a promising novel agent for the treatment of bladder cancer (BCa). Cisurocanic acid (*cis*-UCA) is a natural compound found in the mammalian skin after ultraviolet irradiation. It showed a clear dose-dependent antiproliferative activity against rat urothelial cancer cell lines (AY-27) in vitro, as well as inhibitory effects on tumor growth in the orthotopic rat BCa model in vivo. Considering the

good side-effect profile of *cis*-UCA, it may play a role as an intravesical agent in the future.

Due to high rates of recurrence and progression of non-muscle-invasive BCa, its treatment still remains controversial. Cao and associates² evaluated the synergistic antitumoral effects of interleukin (IL)-12 gene therapy and combined chemotherapy with pirarubicin (THP). BCa cells were cultured and transfected with recombinant plasmid encoding IL-12 genes. Their study showed significantly higher cell death rates in vitro in the group that had been treated with a combination of both therapies. In vivo, a significant decrease in tumor size was achieved by using THP in combination with IL-12 gene therapy. Although further investigation is needed, the additive effect of this novel treatment modality seems to be a promising approach.

Kobavashi and colleagues³ assessed the feasibility of diffusion-weighted magnetic resonance imaging (DWI) in the diagnosis of BCa. The same study group received third place this year for the best abstract in oncology,⁴ honoring their findings in upper urinary tract tumors using the same technique. Regarding BCa, their study compared the diagnostic performance of the DWI with T2-weighted imaging (T2W), which is probably the most accurate imaging modality in detecting BCa. Using a 1.5-T magnetic resonance, not requiring any contrast agents, the sensitivity of DWI was 95%/94%. In the detection of muscle-invasive disease, the sensitivity was 100%/100%, compared with 93%/88% and 100%/96% using T2W, respectively. Therefore, the authors concluded that DWI offers a higher objectivity in detecting BCa lesions.

Prognostic Factors and Outcome

Seiler and colleagues⁵ evaluated the prognostic value of extracapsular extension (ECE) of lymph node metastasis, critically analyzing the total diameter of all metastases as a potential independent risk factor. Their study included 162 lymph node-positive BCa patients (preoperative NOM0) who underwent radical cystectomy and bilateral lymphadenectomy in curative intent. The results showed a 5-year overall survival of the cohort of 33%, as well as 8% and 50% for ECE-positive and -negative patients, respectively. ECE was the strongest independent risk factor, whereas the nodal tumor burden did not add any independent prognostic information. Finally, the study indicated that the important differences between subsets of nodal-positive bladder cancers are not adequately represented in the current Tumor-Node-Metastasis classification.

Regarding risk factors for bladder cancer, a very interesting contribution was made by Garcia-Rojo and

associates.⁶ The effects of urination frequency, water intake, and smoking status were investigated in a large multi-institutional cohort of 884 patients and 996 controls. The authors demonstrated a consistent inverse trend in risk with increasing nighttime voiding frequency in both men and women. Nocturia seems to have a protective effect by shortening the contact time of carcinogens and the urothelium of the bladder, with a significant risk reduction of 40% to 50%, up to 80% in individuals with increased water intake. Increased urination frequency and water intake could diminish the effect of urinary carcinogens, namely, tobacco smoking.

In a large retrospective study, Nuhn and colleagues⁷ analyzed the data of 3973 patients at 9 institutions. Within their study, concomitant carcinoma in situ (CIS) was neither associated with disease recurrence nor with cancer-specific death (regardless of pathologic stage). The study further demonstrated a discrepancy between pathologists in determining the presence of concomitant CIS at the morphologic level.

Another interesting contribution was made by Krause and colleagues.⁸ Their objective was to evaluate the 15-year long-term experience with patients treated in a curative intent with transurethral resection of the bladder tumor (TURBT) in combination with radiochemotherapy (RCT) or radiation (RT) alone. By analyzing the data of 473 patients, they revealed that pT-stage, lymph invasion, residual tumor status after TURBT, local and distant metastasis, kind of therapy, and response rate in the control-transurethral resection (TUR) are significantly influencing the long-term results of TURBT plus RCT/RT. No influence on outcome was seen for associated CIS, grading, and uni- or multifocality.

Management of Non-muscle-Invasive Bladder Cancer

Di Stasi and colleagues⁹ prospectively evaluated the effects of one immediate pre-TUR intravesical instillation of electromotive mitomycin-C (MMC) for primary non-muscle-invasive bladder cancer (NMIBC). In comparison with an immediate post-TUR instillation or TUR alone, patients with multiple, intermediate, and high-risk NMIBC benefit from 1 preoperative instillation of 40-mg electromotive MMC with 20-mA electric current for 30 minutes. This significantly enhanced the disease-free interval and decreased the risk of recurrence.

The European Organisation for Research and Treatment of Cancer Genito-Urinary Group phase II trial 30993¹⁰ evaluated the possible synergistic effect of alkylating MMC and Bacillus Calmette-Guérin (BCG) after the TUR procedure for patients with NMIBC plus CIS. The results showed that both treatment groups (MMC + BCG vs BCG alone) had almost equivalent complete response rates (75.6% vs 73.8%) and outcome. Therefore, it can be concluded that sequential chemo-immunotherapy with MMC + BCG does not show any synergistic effects.

It has been reported that the risk of progression to muscle-invasive disease is increased in T1G3 lesions.¹¹ Urdaneta and colleagues¹² presented data on the location of T1G3 tumors in early and late recurrences, compared with and without BCG instillation. They demonstrated a clear difference in recurrence rate in 2 groups of patients treated with (group 2, 43.8%) or without (group 1, 66.7%) BCG. Within this study, no patient underwent re-TUR and the overall recurrence rate at the same site of the previous TUR was 8.6%. Furthermore, urologists should particularly focus on the same site of the previous resection (38.2% early vs 8.8% late recurrence

rate) in the early postoperative follow-up.

Management of Muscle-Invasive Bladder Cancer

Radical cystectomy (RC) is the standard of care both for tumors invading the muscularis propria (T2+) and for recurrent high-risk non-muscle-invasive lesions (Ta, T1) failing intravesical therapy.¹³ Brausi and colleagues¹⁴ introduced a modified operation technique, which appears to be beneficial in elderly and frail patients. The so-called “mini-invasive anatomical extraperitoneal RC” requires only a small sub-umbilical skin incision of 7 to 8 cm. The complete procedure is done extraperitoneally and in a retrograde fashion. In comparison with the standard transperitoneal approach, superior results regarding mortality (0%), mean blood loss (423 cc), reoperation rate (0/90), local recurrence (2% during mean follow-up of 30.2 months), and mean hospital stay (16 days) were reported in this study.

Burger and associates¹⁵ assayed the value of a complete histopathological processing of cystoprostatectomy specimen in the detection of incidental PCa. By comparing 2 different methods of processing the prostate without any suspicion to PCa, it could be demonstrated that the entire processing of the prostate reveals significant information. Overall detection rate in the thorough-processing group was 40%, compared with 17% in the standard-processing group. Furthermore, tumor stage \geq pT2b ($P = .06$), Gleason score (GS) grade \geq 7 ($P = .036$), and positive surgical margins ($P = .01$) were detected more accurately. This information is needed to individualize follow-up strategies, especially in younger patients.

Distal ureteric malignancy among patients who underwent RC is known to lead to an unfavorable prognosis. The most effective way to determine

this risk factor is to assess the ureteral frozen-section margins for anastomotic recurrence. Gakis and associates¹⁶ evaluated the accuracy of frozen section analysis (FSA) and found out that FSA had a high positive predictive value (95.7%) and serves as an independent predictor of distal ureteral malignancy, in addition to the occurrence of pTis. The authors concluded that ureteral FSA at radical cystectomy is important, particularly in patients with CIS of the bladder.

Jonsson and colleagues¹⁷ from the Karolinska University Hospital, Sweden, presented their oncological and functional results of 39 patients who underwent robotic-assisted radical cystectomy and totally intracorporeal urinary diversion (either orthotopic Studer bladder or ileal conduit). Their study illustrates that this technique is feasible but demanding. The learning curve showed that the median operation time decreased from 512 to 417 minutes, whereas the median number of extracted lymph nodes increased from 18 to 33 after having performed 20 cases. One patient was found to have a positive surgical margin and 3 patients died later on due to metastatic disease (3-23 months). Functional results revealed good daytime continent rates, and 8 of 9 patients who underwent the nerve-sparing procedure reported erections (no association with positive margins). However, these results are only preliminary data and long-term oncological and functional results are awaited.

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Prostate Cancer

Basic Research

Özdemir and colleagues¹⁸ investigated the stroma reaction in mouse xenograft models of PCa bone metastasis. Human osteoinductive PCa cell line C4-2B4 was xenografted into the tibia of severe combined immunodeficiency mice, and

after osteoblast reaction was evident at radiography, ribonucleic acid (RNA) was extracted from the tumor-bearing bone shaft. RNA from intact tibiae of age-matched mice and from cultured C4-2B4 cells served as “mouse-only” and “human-only” controls. After hybridization of each probe onto the whole human and mouse genome array, the complementary deoxyribonucleic acid probe sequences were compared by bioinformatics analysis. Seventy-seven genes that encode extracellular matrix (ECM) proteins were found to be upregulated in the bone stromal compartment by the presence of PCa cells and 3 proteins, namely, periostin, asporin, and hevin, were further analyzed. Real-time RT polymerase chain reaction assays with mouse (stroma)-specific probes confirmed the stromal expression of the 3 genes and their overexpression in the presence of osteoinductive PCa cells. With this remarkable approach, Özdemir and colleagues showed that cancer cells induce expression of ECM proteins in bone marrow stroma and the promising results indicate that upregulated genes may represent potential biomarkers for bone micro/macrometastasis.

Diagnosis and Prostate Biopsy

De La Taille and colleagues¹⁹ prospectively evaluated the prognostic value of PCa antigen 3 (PCA3) in the prediction of initial biopsy outcome and PCa aggressiveness in a multinational study. A total of 516 men with a serum total prostate-specific antigen (PSA) \geq 2.5-10 ng/mL were scheduled for initial prostate biopsy and urine was collected after digital rectal examination. PCA3 scores were determined and compared with biopsy outcomes. A total of 207 men (40%) had a positive biopsy and showed significantly higher PCA3 scores than men with a negative biopsy (69.6 ± 73.9 vs 31.0 ± 46.9 ; $P < .0001$; median values 50 and 18, respectively). With

35 as cut-off, the PCA3 score had a sensitivity of 64% and specificity of 76%. The probability of having a positive biopsy was 2.7-fold higher in men with a PCA3 score ≥ 35 (64%) than in men with a score < 35 (24%; $P < .0001$). A significantly higher PCA3 score was seen in men with biopsy GS ≥ 7 versus < 7 , in patients with positive cores $> 33\%$ versus $\leq 33\%$, and “significant” versus “indolent” PCa according to Epstein criteria.

A newly developed nomogram was presented by Choi and colleagues²⁰ to predict the probability of ECE in localized PCa. In their retrospective study, 446 of 1471 patients with clinically localized PCa had ECE (30%). Age, PSA, biopsy GS, positive core ratio, and maximum percentage of biopsy tumor were shown to be independent predictors of the presence of ECE ($P < .05$) by multivariate logistic regression models. The nomogram was internally validated, showed good predictive probability, and may be useful for preoperative identification of patients with ECE and selection of patients in which nerve sparing radical prostatectomy is oncologically safe and feasible.

Loch and associates²¹ prospectively evaluated PCa in patients with multiple negative systematic random biopsies (SRB). A total of 132 patients with a history of at least 1 series of negative SRB were assigned to a computerized transrectal ultrasound examination. Cancer-suspicious areas were detected by the system via comparison with known and surgically removed carcinomas of the prostate. Targeted biopsies of areas of similarities with cancer patterns were performed and GS was assessed. PCa could be detected in 66 of the 132 patients (50%), with 5 having a GS of 5, 25 of 6, 22 of 7, 8 of 8, and 7 of 9. The results of this prospective study show that significant cancer can be

found in patients with multiple negative SRBs, as that 71.2% of the 66 men with a positive biopsy had a GS 6 or 7 PCa and 22% had a GS of ≥ 8 . Essentially, multiple negative SRBs do not exclude high-grade PCa.

The Surgical Approach

In a multi-institutional study, Beauval and colleagues²² evaluated the pathologic characteristics of prostate specimen after radical prostatectomy (RP) was performed in low-risk patients eligible for active surveillance (AS). A total of 605 men fulfilled the AS criteria (T1c, PSA < 10 ng/ml, 1 positive core with < 3 mm involved, and GS < 7) and were analyzed with regard to pathologic features and oncological outcome. An upward migration in GS was reported in 36.3% of the 605 men who underwent RP and 15% of the patients had a locally advanced tumor. Specimens of 26% of patients showed a nonsignificant PCa on pathologic examination.

Challacombe and coworkers²³ investigated the peri-operative morbidity, functional, and oncological outcome of robotic-assisted radical prostatectomy (RARP) in 65 patients over age 70 years (mean age, 71.9 years). When compared with a younger group (mean age, 60.2 years), results were comparable and the authors concluded that RARP is a safe and effective treatment with good results in men over age 70 years.

The formation of scar tissue at the vesico-urethral anastomotic site leading to anastomotic stricture is a potential complication after RP. Hruza and coworkers²⁴ presented their results on the incidence of anastomotic strictures in 2200 consecutive patients treated with laparoscopic radical prostatectomy (LRP). A total of 4.6% of the patients developed anastomotic stricture, almost all of them occurring within the first 3 years after surgery. Seven parameters were reported in this study to

be risk factors of anastomotic stricture formation, namely, prolonged catheter time for anastomotic insufficiency ($P < .001$), intermittent suture for urethrovesical anastomosis ($P = .001$), surgeon ($P = .029$), operative time > 4 hours ($P = .016$), transperitoneal access ($P = .041$), nonnerve-sparing surgery ($P = .014$), and high body mass index (BMI) ($P = .035$). The overall anastomotic stricture rate after LRP was low, and a low BMI was the only patient-related parameter with a positive impact on anastomotic stricture rates.

Metastatic Disease

Androgen deprivation therapy remains a hot topic in the management of advanced PCa. In the Scandinavian Prostate Cancer Group (SPCG)-5 study²⁵ patients with newly diagnosed PCa were randomized to receive either total androgen blockade (TAB) or polyestradiol phosphate (PEP). No difference could be observed between the treatment groups in terms of biochemical (TAB 10.1 months vs PEP 10.2 months, $P = .58$) or clinical progression-free survival, or in overall (hazard ratio [HR] 0.96, confidence interval [CI], 0.82-1.12) or disease-specific survival (HR 0.9, CI, 0.77-1.08).

In Barcelona, Brasso and colleagues²⁶ presented an analysis of a subgroup of 131 patients, originally included into the SPCG-5 study, to evaluate the prognostic impact of urokinase plasminogen activator receptor (uPAR) in patients with metastatic PCa. They were able to confirm that all 3 forms of uPAR measured in pretreatment serum samples held prognostic information. Highest uPAR levels were associated with shortest survival. In a multivariate analysis uPAR was shown to be an independent prognostic factor with regard to survival. Interestingly, a qualitative interaction between levels of

uPAR and treatment modality with regard to survival could be observed. Patients with the highest levels of uPAR, levels above the median, tended to do better when they were treated with estrogen. The survival was actually 12 months longer when treated with estrogens than with TAB in these patients. They concluded that uPAR is a prognostic factor in patients with metastatic PCa and those high levels of uPAR may discriminate patients with metastatic PCa who would benefit from treatment with estrogens.

Venous thromboembolism is a common complication in patients with malignant disease. Van Hemelrijck and colleagues²⁷ investigated the risk of thromboembolic disease (TED) in a large series of 73,310 men with PCa. Results showed that all groups of men with PCa were at a higher risk of TED. Patients on endocrine treatment had the highest incidence of deep-venous thrombosis and pulmonary embolism among all groups. In conclusion, thromboembolic disease should be a concern when managing PCa patients, particularly for men who are treated with endocrine treatment of localized disease. ■

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