MEETING REVIEW

New findings in bladder and prostate cancer: highlights from the 26th annual congress of the European Association of Urology, March 18-22, 2011, Vienna, Austria

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At the recent annual congress, of the European Association of Urology (EAU), urologists from around the world presented their exciting discoveries related to an array of topics. Besides the huge variety of different sessions and courses, the EAU Section of Uro-Technology (ESUT) transmitted live broadcasts of surgeries from the medical universities of Vienna and Heilbronn, focusing on novel surgical techniques. Unfortunately, this year’s congress was clouded by the environmental disaster and nuclear accident in Japan, which prevented a number of Japanese urologists to attend the congress due to obstacles in travelling. In this brief update, we will highlight some of the findings and the clinical significance of a few of this year’s important abstracts in bladder and prostate cancer.

Key Words: bladder cancer, T1G3, photodynamic diagnosis, radical cystectomy, prostate biopsy

Bladder cancer

Basic research

After having previously established a sensitive in vivo monitoring of tumor development using bioluminescent imaging (BLI), Autenrieth et al1 presented their results using a fractionated intravesical treatment with 213Bi-anti-EGFR-MAb. After orthotopic instillation of human bladder cells in mice and consecutive bioluminescence imaging, radio-immunotherapy with 213Bi-anti-EGFR-MAb was compared to unlabeled anti-EGFR-MAb and untreated mice. The group of animals that were treated three times every 4 days with 0.46 MBq of the novel agent showed reduced tumor size without radiation damage of the normal urothelium, as well as longer survival time of 100 days, compared to 59 days in other groups. Therefore, fractionated intravesical therapy with the alpha-emitter 213Bi coupled to an anti-EGFR-MAb might be a promising approach, especially for the treatment of advanced stage bladder cancer (BC).

Whereas the Ral signaling pathway, one of the Ras subfamily small GTPases, is involved in the mechanism of invasion and metastasis in BC, the RalGTPase activating proteins (RalGAPs) are known to inactivate small GTPases of Ral. Saito et al2 presented the first report which shows a tumor suppressive function...
for RalGAPs in human cancer. Loss of RalGAPα2 expression was clearly related to the aggressiveness of BC cell lines; RalA/B were higher in high grade BC cell lines with low α2-expression. The authors concluded that RalGAPα2, being the inactivator of Ral small GTPase, is a metastasis suppressor of BC.

As microtubules are one of the most effective targets in cancer therapy, taxanes are currently under supervision for intravesical chemotherapy for patients with BCG refractory non-muscle invasive BC. The group of Mugabe et al. evaluated the in vivo efficacy and safety of mucoadhesive nanoparticulate docetaxel and paclitaxel loaded hydrophobically derivatized hyperbranched polyglycerols for intravesical BC therapy. Besides absent systemic absorption and equivalent cytotoxicity compared to the commercial formulations of Taxol and Taxotere, both taxane formulations showed a significant decrease in tumor cell growth, with the strongest anti-tumor effect after a single intravesical instillation with mucoadhesive docetaxel. This preclinical proof-of-principle should certainly be followed by early phase clinical trials in patients refractory to standard intravesical therapy.

Prognosis, diagnosis and staging

Tilki et al. evaluated the prognostic significance of pT3 substaging in lymph node negative patients with bladder cancer. By analyzing the data of 808 patients with pT3 tumors and a median follow up of 45 months, similar recurrence-free and cancer-specific survival could be shown for lymph node positive pT3a versus lymph node negative pT3b patients. However, in patients with pathologically negative lymph nodes, pT3b substaging was significantly associated with shorter 5 year survival rates and worse outcome. Therefore, pT3 and the definition of macroscopic perivesical fat extension (pT3b) may help to identify patients who could benefit from adjuvant chemotherapy. Interestingly, the group of Dinçel et al. did not find any significant differences in disease-specific and overall-survival rates, comparing the data of 74 patients with lymph node negative pT3a versus lymph node positive pT3b BC. Therefore, the effect on substaging T3 cases on survival and prognosis remains a controversial topic.

Despite the increasing number of studies in recent years on urine-based tumor markers and tests, their use as diagnostic tools in BC remains of limited use. The UroScreen study group of Feil et al. prospectively observed 1772 chemical workers with former exposure to aromatic amines, in order to assess the predictive value of three different tests, namely UroVysion, NMP22 and urine cytology. Their results demonstrated the diagnostic validity of tumor marker tests for early diagnosis of BC in asymptomatic persons at high risk. Especially the combination of cell-based (UroVysion, cytology) and protein-based (NMP22) markers could improve sensitivity and specificity of urine-based markers in screening high risk populations.

By using the Netherlands Cancer Registry, the group of Ploeg et al. analyzed 50,427 patients with BC, in order to evaluate the risk of second primary cancers (SPC). Familial clustering of BC suggests a genetic component and particular sequence variants are known to be associated with cancer risk. The analyses for the risk of SPC were performed at the day of BC diagnosis and 6 months later. Besides the elevated overall risk of SPC, the risk of developing breast, lung, renal pelvis, ureter and urinary tract cancer was particularly increased in BC patients. Furthermore, younger patients (< 50 yr) and patients treated previously with radiotherapy and/or chemotherapy showed an elevated risk of developing SPC. Urologists should be aware, although it may be due to the effect of shared lifestyle, genetic risk factors or late side effects of treatment.

Non-muscle invasive bladder cancer

Recurrence and progression are still the main concerns in the management of T1 high grade (T1G3) tumors. Palou et al. retrospectively evaluated differences in recurrence, progression to invasive disease and cancer-specific survival (CSS) in a cohort of 1039 patients with T1G3 tumors. The authors reported that patients with the intravesical instillation of Bacillus Calmette-Guerin (BCG) Connaught 81 mgrs induction course plus maintenance therapy showed lower recurrence and progression rates (p < .001, resp.), as well as longer CSS (p = .003), compared to TUR only, Re-TUR only, BCG 21 mgrs and 81 mgrs without maintenance therapy. This leads to the conclusion that full dose BCG treatment with maintenance should be performed in T1G3 patients.

This year’s second best abstract in oncology was dedicated to the work of O’Brien et al., who presented a prospective randomized trial comparing hexylaminolevulinate (Hexvix) assisted “blue-light” (B/L) TUR plus a single shot of intravesical mitomycin (MMC) versus conventional “white-light” (W/L) TUR plus a single shot of MMC. Although photodynamic diagnosis (PDD) with Hexvix is known to provide a more complete diagnostic assessment of non-muscle invasive bladder cancer (NMIBC), their trial could not report a reduction of the recurrence rate in the
PDD group. For their 249 randomized patients with NMIBC (129 B/L versus 120 W/L), no statistically significant difference in recurrence (being the endpoint of the study) could be observed at 3 (p = .86) or 12 months (p = .5). However, the diagnostic role of PDD in carcinoma in situ patients remains unquestioned.

Regarding recurrence of NMIBC, another interesting contribution was made by Blázquez et al.\textsuperscript{10} from Spain. The weight of the resected tumor specimen from TUR was introduced as being an objective, measurable and reproducive prognostic factor for tumor recurrence. By retrospectively analyzing the specimen of 423 patients diagnosed with NMIBC and a median follow up of 58 months, the median weight of specimen was 7.5 grams (.7 g-.70 g). The multivariable analysis showed the weight as an independent variable for recurrence (p = .007) with tumors larger than 4 grams having a 2.6 times higher risk of recurrence than tumors with lower weight, as it was demonstrated in a ROC curve analysis (HR 2.6, 95% CI, 1.3-5.2). This novel aspect has not been described so far and constitutes a promising approach in the prediction of tumor recurrence.

Besides the conventional wire-loop transurethral resection of the bladder tumor (TURBT), new techniques of dissecting the tumor are gaining acceptance. As it is already used in the gastrointestinal tract, the application of a water jet dissector was prospectively evaluated by Fritsche et al.,\textsuperscript{11} combining it with needle-knife dissection (HybridKnife). By resecting 30 urothelial tumors in 17 unselected patients, a water beam pressure of 30 bars was used within an angle of 20°-90°. The HybridKnife was able to dissect all tumors from the bladder wall en bloc, showing no perforation and an equivalent learning curve to common techniques. Although it seems to facilitate the histopathological assessment, the oncological outcome remains unclear and should be evaluated in further studies.

Muscle invasive bladder cancer

Radical cystectomy (RC) is the standard of care both for muscle invasive bladder cancer (MIBC; stage T2+) and for recurrent high risk NMIBC failing intravesical therapy. However, the necessity of an extended bilateral pelvic lymph node dissection (BPLND) in unilateral BC is under debate due to the fact that contralateral lymphatic drainage in the endopelvic region has not yet been demonstrated. The group of Roth et al.\textsuperscript{12} assayed the value of BPLND in strictly unilateral BC. Forty patients were preoperatively injected Tc-99m nanocolloid into the non-tumor-bearing lateral bladder wall, in order to detect radioactive lymph nodes (LNs) with a single photon emission computed tomography (SPECT) fused with conventional CT. An intraoperative gamma probe was then taken during BPLND to confirm the SPECT-CT detected LNs. By generating a three-dimensional model of each LN site, it could be demonstrated that cross-over is a common phenomenon but may be limited to the contralateral obturator fossa, external iliac and common iliac region. There was no proof of radioactive LNs in the contralateral internal iliac region. Therefore, it can be concluded that bilateral extended PLND is mandatory even in strictly laterally sited tumors.

Jonsson et al.\textsuperscript{13} from the Swedish Karolinska Institute presented their oncological outcome of 56 patients who underwent robotic assisted radical cystectomy (RARC), PLND and totally intracorporeal either orthotopic Studer or ileal conduit urinary diversion (UD). The authors reported clear surgical margins in 98.2% of their patients, as well as mean number of 23 (SD ± 10, 10-52) extracted LNs for the whole series and 33 (SD ± 9, 19-52) for extended PLND. Three patients died postoperatively (after 13, 23, 35 months) due to metastatic disease. One patient had to undergo urethrectomy and conversion to an ileal conduit due to recurrent malignancy. However, these results illustrate RARC with intracorporeal UD as a feasible option with acceptable oncological outcome and excellent lymph node count when performing extended PLND.

Nomograms can constitute a helpful tool in outcome prediction of cancer patients. Gakis et al.\textsuperscript{14} introduced a new scoring-model ("TNR-C score"), based on standard pathological risk factors, as well as on the inflammatory marker C-reactive protein (CRP). After a median follow up of 30 months, the data of 246 patients revealed elevated baseline CRP levels (defined as > .5mg/dL) as being significantly associated with advanced tumor stage, increased lymph node density, tumor size, age and positive resection margins (all: p < .03). As shown in multivariable analysis, CSS was significantly lower in patients with elevated CRP, advanced tumor stage, increased lymph node density and positive resection margins. Based on regression estimates of significant parameters, the CRP-based TNR-C score showed a 3 year CSS rate of 80.5%, 44.9% and 7.1% in patients with a score of 0-2, 3-6 and 7-10, respectively (model: p < .001). The accuracy of the TNR-C score confirms the predictive value of preoperative CRP for BC and therefore constitutes a useful nomogram for predicting outcome.
Main points

• Second primary cancers more often occur in younger patients and those after chemo/radiotherapy, most frequently affecting breasts, lungs, renal pelvis, ureters and the urinary tract.
• In T1G3 tumors, full dose BCG instillation (81 mgrs) with maintenance therapy should be performed.
• Although TUR with PDD is known to provide a more complete diagnostic assessment, it does not offer a reduction in recurrence rate.
• Recurrence rate of NMIBC is associated with the weight of the resection specimen (elevated risk > 4 g).
• RARC with PLND and intracorporeal urinary diversion shows acceptable outcome and lymph node count.
• Extended PLND is mandatory even in tumors that are strictly laterally sited.
• Preoperative C-reactive protein may be useful in predicting outcome of BC patients

Prostate cancer

Basic research

This years first prize for the best abstract in oncology was given to the group of Ricci et al\(^1\) for their work on prostate cancer stem cells. In a prospective study, the group analyzed the percentage of cells positive for markers of stem cells in the hematopoietic bone marrow of patients with prostate cancer. The percentage of positive cells has shown to correlate with bone metastatic progression in previous studies. CD45-/ alpha2+/alpha6+/c-met+ cells from bone marrow aspirates in 12 healthy donors (control group) and 120 patients with prostate cancer were analyzed and quantified. Prostate cancer patients were divided into four groups: patients in Group 1 had clinically localized disease (T1-2), patients in Group 2 showed biochemical progression after primary tumor treatment, patients in Group 3 had metastatic prostate cancer that was androgen-sensitive and patients in Group 4 were hormone refractory. The percentage of cells positive for these markers were particularly high in hormone-refractory patients in Group 4 and also significantly higher in patients who showed evidence of bone metastases upon follow up. In addition, the percentage of c-met+/alpha2+/alpha6+ cells in the bone marrow of prostate cancer patients significantly correlated with prognosis. These promising results suggest the release of cells with “stem cell like” phenotype from the primary prostate cancer as an early event in metastatic progression.

The Japanese group of Yokomizo et al\(^2\) braved the obstacles in travelling, contributing an excellent study that won this year’s third prize for best abstract in oncology. In their study the group investigated the underlying molecular mechanisms of statins in the regulation of PSA, the androgen receptor (AR) and cell proliferation in prostate cancer cell lines. Based on epidemiological data that suggests a decrease in prostate cancer risk and a reduction in serum PSA by statins, they investigated the regulatory mechanisms of statins in three prostate cancer cell lines. Results show that statins reduced cell proliferation only in AR positive but not in AR negative cells, suggesting that cell proliferation is modulated by statins via AR expression. Statins decrease AR protein levels via proteolysis, while mRNA transcription is not affected. In addition, the decrease of AR protein levels was associated with a reduction in androgen sensitivity and a decrease in cell proliferation. Finally, down regulation of the AR protein and reduce in androgen sensitivity could be one of the molecular mechanisms to explain the reduced prostate cancer risk in patients treated with statins.

Diagnosis and screening

Kemppainen et al\(^3\) analyzed the associations between the use of antihypertensive agents and prostate cancer incidence. In their large population based study, the Finnish group identified all newly diagnosed men with prostate cancer during 1995 to 2002 and matched controls. Information on the purchase of antihypertensive drugs during the study period was accessed at the prescription database of the Social Insurance Institution of Finland. In contrast to findings of previous epidemiological studies that suggested a possible reduction in the risk of prostate cancer for the use of calcium-channel blockers and ACE-inhibitors, the ever-use of antihypertensive drugs was marginally associated with increased risk of prostate cancer (OR 1.16, 95% CI, 1.12-1.21). However, the risk of advanced prostate cancer was equal for both groups (OR 1.08, 95% CI, .98-1.18). Interestingly, the subgroup of patients treated with calcium-channel blockers had a slightly lower risk of prostate cancer (OR .77, 95% CI, .63-.94). In conclusion, the authors stated that the observed increase in risk of prostate cancer might be biased due to systematic differences between medication-users (who tend to be more active in terms of medical check ups) and non-medication users. The EAU guidelines help urologists to make decisions in every day practice and provide access to the best contemporaneous consensus view on the
most appropriate management currently available. Heidenreich et al\textsuperscript{18} retrospectively evaluated the EAU guideline compliance (EAU-GC) of urologists in the management of 885 patients with organ-confined prostate cancer with regards to diagnosis, staging and treatment. Patients that were treated between the years 2006-2007 (Group 1), 2008-2009 (Group 2) and 2010 (Group 3) were included in the analysis. Results show that regarding the number of biopsies taken, the EAU-GC increased from 17.8% in Group 1 and 34.2% in Group 2 to 80.4% in Group 3. Concerning the frequency of CT, MRI and bone scans related to the D’Amico risk profile for staging of prostate cancer, the EAU-GC was only 75% for low risk, but almost 100% for high risk prostate cancer patients. However, with regard to the way prostate biopsies are processed, the EAU-GC is low with pathology report stating EAU-GC in only 27% of the specimen. Clearly, the communication between urologists and pathologists is in need of improvement and collaborations with societies of pathology are desirable.

The surgical approach

Since its introduction in 2000, the robot-assisted approach to radical prostatectomy has emerged to a widely used treatment modality for patients with organ-confined prostate cancer. However, data on long term oncological and functional outcomes are sparse. At this year’s congress, Suardi et al\textsuperscript{19} presented the oncological outcomes of robot-assisted radical prostatectomy (RARP) in 184 consecutive patients with 5 years of follow up. Histological examination of specimens showed organ-confined disease in 117 (62.5%), extracapsular extension in 56 (30%) and seminal vesicle invasion (SVI) in 14 patients (7.5%). At final analysis 5 years after surgery, one patient had died from prostate cancer and 10 patients from other causes. The 5 year biochemical recurrence free-survival was significantly higher in patients with negative surgical margins when compared to patients with positive margins (87\% versus 68\%, p < .001). The biochemical recurrence-free survival rate after 5 years was 90\% for patients with organ-confined disease and 84\% for patients with extracapsular extension. In contrast, only 43\% of patients with SVI were alive and free of biochemical recurrence 5 years after surgery. The presence of SVI was shown to be the strongest predictor of biochemical recurrence on multivariable analysis.

Trinh et al\textsuperscript{20} reported on the complications after RARP in 3317 patients. Surgery was performed at a tertiary referral center by two experienced surgeons and three beginners. Of the 3317 patients who underwent RARP complications occurred in 302 patients (9.1\%). A total of 349 complications were observed with 81 medical and 268 surgical in type. Of all complications 223 were minor (Clavien classification I-II) and 126 major (Clavien III-IV). Almost 80\% of complications occurred within the first month of surgery. In addition, only cardiac diseases have shown to be predictive for medical complications, whereas cardiac, hepatic and gastrointestinal comorbidities and positive lymph node status were predictive for surgical complications. RARP showed a good safety profile and a complication rate of 9\%.

The significantly lower blood loss and the smaller incisions that result in lower pain scores are undoubtedly advantages of minimally invasive RP compared to the open approach. An interesting contribution by Amaruch et al\textsuperscript{21} was the report on the feasibility and safety of 24 hour hospital stay for laparoscopic radical prostatectomy (LRP). The group evaluated 258 consecutive patients who underwent LRP. Of all patients included, 78 (30.2\%) were discharged in less than 24 hours and none of these patients required blood transfusions or experienced early or late complications. Lymphadenectomy, previous abdominopelvic surgery and diabetes mellitus have shown to be independent predictors of a hospital stay longer than 24 hours.

Oezdemir et al\textsuperscript{22} evaluated various molecular markers in lymph nodes of patients undergoing radical prostatectomy (RP) with extended pelvic lymph node dissection (PLND). Primarily, marker expression was analyzed in lymph nodes of patients of both gender who were undergoing lymph node dissection for benign and malignant diseases. After selection of eligible markers, lymph nodes of 13 patients who underwent RP with extended PLND were analyzed for these markers by RT-PCR. These findings were then correlated with histopathological results. Three of the 13 patients had pathologically confirmed positive lymph nodes and PSA, AR, EPCM and PSCA were found to be expressed. Two of these three pN1 patients had 7 lymph nodes that were expressing these markers but were negative on histopathological examination. In addition, 5 of the 10 patients that were negative for lymph node metastasis on histopathological examination had lymph nodes that were expressing the markers. These interesting findings suggest a role of PSA, EPCM and PSCA in the evaluation of lymph nodes in patients undergoing RP with extended PLND and warrant further investigation.

Although PLND has a substantial role in diagnostic staging for patients with prostate cancer, complications...
such as lymphocele, lymphoedema, vascular injury, nerve injury, ureteral injury and thromboembolic events may occur. Damage of the pelvic plexus during extended PLND might affect erectile function (EF) after surgery. Bianchi et al. analyzed EF recovery of 722 patients treated with bilateral nerve-sparing radical prostatectomy (BNSRP) and divided them into three groups. Patients in Group 1 did not undergo PLND, patients in Group 2 had less than 20 and patients in Group 3 had more than 20 lymph nodes removed. After stratification for age, PSA, clinical stage, biopsy Gleason score and preoperative EF, the extent of PLND was not associated with EF recovery. Furthermore, EF recovery rate did not differ significantly in the three groups at 1 and 2 years after BNSRP. In conclusion, age and preoperative EF are still the strongest predictors of EF recovery after surgery for organ-confined prostate cancer.

Being in charge of the EAU Section of Oncological Urology (ESOU), Professor Bob Djavan from New York discussed the topic of frozen section analysis (FSA) in radical prostatectomy. He stated that FSA of pelvic lymph nodes is often inaccurate and does not influence the treatment decision, as even patients with positive nodes would benefit from surgery in most of the cases. In general, it should only be performed when the results changes the therapeutic approach. Even FSA of the margin status in high risk patients would only be useful in the selected group of nerve-sparing procedures. Therefore, we should clearly abandon the “frozen section lymph nodes and close if possible” philosophy during radical prostatectomy.

Metastatic disease

The treatment of metastatic castrate resistant prostate cancer (mCRPC) after progression on first-line docetaxel chemotherapy remains a challenging task for the clinician with limited therapeutic options. Nevertheless, new therapeutic targets have been identified and novel substances are currently under investigation. Fizazi et al. presented the results of a multi-institutional, randomized, double-blind, placebo-controlled phase III study, comparing abiraterone acetate (AA) with prednisone (P) to placebo with prednisone. AA is an orally administered inhibitor of CYP17A1 that reduces serum testosterone levels to castration levels via inhibition of testosterone synthesis in the adrenal gland. A total of 1195 patients with mCRPC were randomized 2:1 to receive either AA 1000 mg + P 5 mg bid or placebo + P bid. The median overall survival (OS) was 14.8 months in the AA+P group and 10.9 months in the placebo group (p < .0001). Also, median time to PSA progression (TTPP), median radiographic progression free survival (rPFS) and PSA response were significantly better in the AA+P group than in the placebo+P group (p < .0001). AA+P has shown to significantly improve OS, TTPP, rPFS and PSA response, was well tolerated and may provide a new therapeutic option for patients with mCRPC after progression on docetaxel treatment.

Main points

- EAU guideline compliance with regards to processing prostate biopsies is low and needs to be improved.
- Five year biochemical recurrence free survival in patients treated with RARP is 90% for patients with organ-confined prostate cancer.
- RARP is a safe surgical procedure with a complication rate of about 9%.
- The extent of PLND does not affect erectile function recovery rate in patients treated with bilateral nerve-sparing radical prostatectomy.
- Frozen section analysis of LN should only be done when the results changes therapeutic approach.
- Abiraterone acetate is a promising novel agent for patients with mCRPC after first line docetaxel failure.

Disclosure

The authors have nothing to disclose.

References


