Embracing Excellence in Prostate, Bladder and Kidney Cancer
2nd European Multidisciplinary Meeting on Urological Cancers
27-29 November 2009, Barcelona, Spain

2nd European Meeting on Urological Cancers (EMUC)

Presented by

Meeting Report

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Introduction

Based on the success of the first European Meeting on Urological Cancers, the second EMUC was organized by the European Association of Urology (EAU), the European Society for Medical Oncology (ESMO) and the European Society for Therapeutic Radiology and Oncology (ESTRO). The EMUC Organizing Steering Committee and Scientific Committee put together an inspiring program which covered the entire multidisciplinary spectrum of bladder, prostate, renal and testicular cancer. Moreover, for each tumor type, state of the art lectures, hot topics and future goals were presented by excellent speakers. The participants of the meeting numbered over 1100 and had different professional backgrounds (61% urologist, 11% radiation oncologist, 11% medical oncologist, 17% other). The multidisciplinary program provided updates on the management of kidney, prostate, bladder and testicular cancers and simulated the atmosphere of a university college.

Prostate Cancer

Preventive Screening

There is level I evidence that a prostate cancer screening program for men aged 55–69 years can reduce the risk of prostate cancer mortality. The number of men needed to screen in order to prevent 1 prostate cancer death is 1410. Out of these men, 1068 can be expected to comply with screening and 48 would need treatment. In comparison, for the prevention of 1 breast cancer death 1000 women need to participate in screening and 6 women would need treatment. The high overtreatment rate in prostate cancer screening is due to the fact that the prostate specific antigen (PSA) level does not discriminate between indolent and aggressive prostate cancer.

Practice points and future research opportunities
The screening yield should be improved by the use of screening nomograms, such as the risk indicator 3 (www.prostatecancer-riskcalculator.com; Prostate Cancer Research Foundation (SWOP) 2008, 2nd Edition), or by the use of more specific markers. The decision whether or not to initiate prostate cancer screening should not only be guided by the number needed to screen and the burden of overtreatment, but also prevention of co-morbidity due to advanced disease should also be taken into account. The high number of indolent/low stage prostate cancers detected by screening urges clinicians to evaluate safety and efficacy of active surveillance programs and focal therapies, such as cryoablation and brachytherapy.

Prostate cancer work up

Transrectal ultrasound facilitates measurement of prostate cancer size, even with improved techniques, such as color doppler and contrast-enhanced ultrasound, has a low specificity for cancer. Furthermore, its reliability is investigator/learning curve-dependent. Magnetic resonance imaging (MRI) has a higher specificity for cancer and the chance of a falsely low Gleason score is smaller. Therefore, MRI could be very useful in guiding biopsy procedures. Depending on prostate size, at least 10 (particularly lateral) core biopsies should be performed. MRI-guided biopsy is indicated in case of laterally located suspicious lesions, which appear difficult to reach.

For the detection of lymph node metastasis, a Fe-nanoparticles MRI appears to be the most sensitive and specific procedure, but the screening pharmacon is currently not available.

For the detection of bone metastases, MRI has been shown to have a considerably higher sensitivity and specificity than bone scan.

Adjuvant therapy for high risk localized prostate cancer

- Three phase III randomized controlled trials (RCTs) have confirmed the benefit (10-year metastasis-free survival 83% vs. 61%) of adjuvant radiotherapy.
  The results of a subgroup analysis by the German multicenter trial were reported by Wiegel. The impact of radiotherapy appeared highest in patients with positive surgical margins above 3 mm and in patients with less than 2 mm extraprostatic tumor extension. In spite of the statistical evidence, patients are often not referred for adjuvant radiotherapy.
- Adjuvant androgen deprivation therapy (ADT) has been shown to improve prostate cancer specific overall survival. In most trials with a positive outcome ADT was given for a period of at least 2 years.
- The value of adjuvant chemotherapy is currently under investigation.
  - Mitoxantrone does not appear to produce additive benefit, when given in combination with ADT. Furthermore, there have been reports on an excess number of acute leukemias.
  - Docetaxel is currently being tested in different RCTs (docetaxel vs. placebo; docetaxel/ADT vs. ADT; docetaxel/radiotherapy vs. radiotherapy). The CALGB-90203 trial is evaluating the value of docetaxel in the neo-adjuvant setting.

Practice point
In case of radical prostatectomy adjuvant radiotherapy should always be considered.

Clinical T3-disease: radical prostatectomy or curative radiotherapy?

- Radical prostatectomy
  Radical prostatectomy and curative radiotherapy have never been compared in a prospective RCT. Historical data suggest that cancer-specific survival is comparable for both treatment modalities.
  Potential advantages of prostatectomy are best local control for over-staged T2-disease (which occurs in 25% of patients with clinical T3 disease), surgical co-morbidity comparable to co-morbidity after intervention for T1/T2 disease and avoidance of complications known to develop after radiotherapy.
  Adjuvant radiotherapy has been shown to improve survival in patients with pT3N0M0 prostate cancer (P=0.023). A disturbing adverse effect of radical prostatectomy is erectile dysfunction, which is caused by penile hypoxia (due to injury of cavernous nerves) and loss of smooth muscle cells. Silfenadil has been shown to improve postoperative erectile function in comparison with placebo. In a recently reported trial,

the benefit of vardenafil was comparable between patients on daily medication and those who took the medication on demand.

- Radiotherapy
  In case of radiotherapy, 6 months of adjuvant hormonal therapy are considered obligatory. In a recently published RCT by Bolla et al., (Lancet 2002;360:103) the difference in the effect of short-term and long-term androgen suppression on 5-year mortality was modest, but the authors reported that the advantage of long-term suppression is likely to be maintained at 10 years, whereas the benefit of short-term suppression may have dissipated by then. They recommended radiotherapy plus long-term androgen suppression for men with locally advanced prostate cancer (classified as stage T2c or above, with a WHO performance status of 0 to 2) who have no contraindicating coexisting conditions.

  Radiotherapy devices which adjust to prostate movement (indicated by a rectal balloon or intraprostatic gold markers) are considered the gold standard.

  Current research is aimed at dose escalation, hypofractionation and partial volume irradiation. Dose escalation, which should be performed by means of Intensity Modified Radiotherapy (IMRT), is related with increased cytotoxicity, but late rectal and urinary toxicity occur more often.

  Hypofractionation - i.e. delivery of an iso-effective dose with larger fractions, but a smaller fraction number - has the advantage of faster dose delivery and lower costs. In a Phase III RCT by Saracino et al. (EMUC, 2009) 20 fractions of 3.1 Gray (Gy) instead of the usual 40 fractions of 2 Gy resulted in a higher 3-year recurrence-free survival [88% vs. 82%; not significant (NS)]. Early and late toxicity figures were comparable. Further hypofractionation also appears feasible, as was presented by Aluwini et al. (EMUC, 2009) (4 Cyberknife fractions of 9.5 Gy) and Bolzicco et al. (EMUC, 2009.) (5 Cyberknife fractions of 7 Gy).

Practice point and future research opportunities
Prospective RCTs should point out which radiotherapy schedule offers the optimal combination of treatment benefit, treatment duration and adverse effects.

Salvage radiotherapy

In case of subclinical PSA-increase after prostatectomy, 54% of patients have local recurrence, whereas 46% have distal recurrence. For patients with loco-regional recurrence retrospective data suggest that upfront salvage radiotherapy (PSA < 0.5) produces superior results in comparison with radiotherapy initiated after a certain period of expectancy. Combined modality treatment including hormonal therapy is not considered standard.

Practice point and future research opportunities
RCTs should point out whether patients who undergo salvage radiotherapy can benefit from dose escalation and/or hypofractionation.

Locoregional recurrence after radiotherapy

PSA recurrence is defined as any increase of 2 ng/ml or more above the nadir PSA. Depending on risk stratification at the start of radiotherapy 5-year PSA relapse-free survival percentages range from 47% to 91%. In case of recurrence radical prostatectomy, brachytherapy, cryotherapy and high intensity focused ultrasound (HIFU) could be considered as salvage treatment options. There is no consensus regarding the optimal salvage treatment because of the lack of evidence based literature.

New approaches in hormonal therapy

- Luteinizing hormone-releasing hormone (LH-RH) agonists initially lead to an androgen rise, which causes a clinical flare up and sometimes a temporary increase of complaints; castration levels of testosterone (defined as 20 ng/dL) are not reached in 46% of patients. LH-RH antagonists lead to a more pronounced down-regulation of testosterone, do not produce a flare up and do not need to be combined with an anti-androgen. The LH-RH antagonist degarelix has been shown to significantly improve PSA progression-free survival in comparison with leuprolide (CS-21 trial). Moreover, the side-effect profile was more favorable.
- Anti-androgens target the androgen receptor, but the transcription blockade of androgen-responsive genes is far from optimal.
  - Abiraterone inhibits residual androgen biosynthesis in adrenal glands and tumor cells. Its therapeutic value for patients with castration-resistant advanced prostate cancer is currently being tested in Phase III.
  - MDV3100 has a 5 times higher affinity for the androgen receptor than bicalutamide. A phase II study has shown a 36% (9/25 patients) response rate in castration-resistant chemotherapy-naive patients. In castration resistant patients who had received prior chemotherapy 12% (4 out of 34 patients) partial responses and 53% (18 out of 34 patients) stable disease were achieved. A phase III placebo-controlled RCT has recently begun patient inclusion.

Practice points and future research opportunities
New classes of agents, such as LH-RH antagonists, androgen synthesis inhibitors and stronger androgen receptor blockers are expected to improve outcome in patients with prostate cancer and the term castration resistant may eventually need a new definition.

How to treat bone metastases?

- Medical treatment
  Up to 65% of patients with prostate cancer eventually develop bone metastases, which can cause bone pain and fractures, resulting in invalidation. Pathological fractures are related with an increased risk of death. Skeletal related events (SRE) occur in 49% of untreated patients. Bone damage is mediated by tumor-produced cytokines, such as interleukin(IL)-6 and parathyroid hormone-related protein (PTH-RP), which increase osteoclast activity. Osteoclasts on their turn produce IL-6 and transforming growth factor(TGF)-beta, which increase tumor cell proliferation.
  - Bisphosphonates are resorbed by osteoclasts, which leads to loss of function and cell death. The in vivo inhibiting potency of zoledronic acid is 1000 times stronger than the inhibiting potency of pamidronate. In a placebo-controlled RCT pamidronate has not been shown to reduce the percentage of SREs, whereas treatment with zoledronic acid leads to a 32% risk reduction. Patients with decreased renal function should be treated with a lower dose and cautiously followed. A dental check up before treatment may decrease the risk of jaw osteonecrosis.
  - Receptor activator of nuclear factor-kappa B (RANK) ligand is produced by osteoblasts in response to tumor cell stimuli, which leads to increased bone resorption. Denosumab binds to RANK ligand and, in phase II a monthly subcutaneous injection of 60 mg, resulted in a strong reduction in bone resorption. In a recently reported Phase III trial (Smith et al. NEJM 2009; 361:745–755) the addition of denosumab to ADT in patients with non-metastatic disease led to an increase in bone volume and a reduction in the percentage of SREs. Two placebo-controlled palliative RCTs have recently been closed for inclusion and the results are eagerly awaited. In one trial castration resistant patients with advanced prostate cancer, but without bone metastases, have been included. In the other trial castration resistant patients with bone metastases have been included and time to SRE is the primary endpoint.

Practice point and future research opportunities
Future trials should clarify the position of bisphosphonates and RANK ligand inhibitors to determine which one is the first choice or whether a combination may be the most effective treatment.

- Radioisotopes
  Bone directed radioisotopes could be administrated for the prevention of SREs or palliation.
  - Strontium^{89} (beta particles) is as effective as external beam radiotherapy in alleviating bone pain, but reversible platelet and white blood cell toxicity occurs more often.
  - Samarium^{153} has a higher activity and requires less time to achieve a response, but the radiation hazard (beta and gamma radiation) is higher.
  - Alpha particles differ strongly from beta particles and uptake is much higher in bone metastases than in normal bone. This makes Radium^{223} a very good candidate for radioisotope treatment. Phase I and II studies have confirmed safety and efficacy of Radium^{223} and the ALSYMPCA study (n= 750), which randomizes patients with symptomatic bone metastases between Radium^{223} treatment and placebo, is currently underway.

Bladder Cancer

Non-muscle invasive bladder cancer

The quality of a transurethral bladder cancer resection (TURB) depends on the quality of anesthesia, equipment and skills. The bladder should not be kept over-distended, hemostasis is critical, the procedure should be planned upfront and resections should be recorded on video and reviewed. Training has been shown to decrease recurrence rate from 8–28% to 3–16% (Brausi et al. Eur Urology Supp 2008; 7:549–556).

Fluorescence-guided endoscopy significantly improves the detection of Ta/T1 tumors compared to white light cystoscopy with a higher number of tumors resected and a lower recurrence rate. The use of this equipment is advocated by the EAU (Grade C recommendation).

Practice point and future research opportunities
Newer techniques, such as narrow band imaging, optical coherence tomography and Raman spectroscopy, may lead to a better visualization of Ta/T1 tumors and eventually obviate the need for adjuvant bladder installations.

Muscle invasive bladder cancer

- Robotic surgery
  A significant proportion of patients with bladder cancer are 75 years or older. For such patients, cystectomy can provide a favorable outcome, as long as there is no serious co-morbidity. There is a strong trend towards laparoscopic cystectomy in order to decrease the impact of the operation and the complication rate. Urological surgeons are being pushed to perform robotic surgery, in particular with the Da Vinci robot, which is thought to further minimize the invasive procedure. Claimed advantages are shorter operating time, less blood loss, less postoperative pain, shorter hospital stay and less physical strain for the surgeon. Disadvantages are the high costs and the required learning curve. Robotic surgery appears safe, although publication bias cannot be excluded, and oncologic long-term follow up data are not available. An International Robot-Assisted Cystectomy Consortium (IRCC) has recently been founded in order to further standardize the introduction of robotic cystectomy in everyday practice.

- Neobladder formation is preferred to ileal conduit
  Patients with an ileal conduit have a significantly decreased quality of life compared to those who have received a continent urinary diversion (McGuire, Ann Surg Oncol 2000; 7: 4–8). Continent urinary reservoirs are most frequently constructed from ileum or sigmoidal colon. Ileal neo-bladders provide the highest reservoir capacity and the highest percentage of patients with nighttime continence, but patients should be regularly screened for urine sterility, voiding function (capacity and residual urine), vitamin B12 deficiency and metabolic acidosis.

- Cystectomy for cT4 bladder cancer
  There are only two retrospective reports (covering only 38 patients) on the outcome of cystectomy for patients with T4 bladder cancer. Hofner reported the results of a retrospective study which included 194 patients derived from a multicenter database with follow up information on 1,950 patients who had undergone a cystectomy. In a Cox-proportional hazards regression analysis the presence of nodal metastases was related with poorer survival (P=0.015) but the number of metastases did not appear to matter. Adjuvant chemotherapy improved survival (P=0.031). In patients with nodal metastases, adjuvant chemotherapy almost doubled survival (median cancer specific survival 28.9 months vs. 15.55 months; P=0.004). Drawbacks of the study are the absence of a central pathological review, lack of information on the extent of lymphadenectomy, possible selection bias and the variety of adjuvant chemotherapy regimens applied.

- Radiotherapy
  A Cochrane analysis has shown a survival benefit for cystectomy compared to radiotherapy, but negative selection (due to patient refusal of surgery) may have biased the analysis. The quality of radiotherapy has been further improved over the last decennium (e.g. bladder movement adjustment, optimization of dose delivery).
- Neoadjuvant therapy
  There is no statistical evidence that preoperative chemoradiation can render locally advanced tumors operable, or that chemoradiation facilitates selective bladder preservation.
  - Three small 3 RCTs (*n*=44, *n*=92, *n*=124) compared preoperative radiotherapy (5 times 4 Gy) followed by cystectomy with cystectomy alone. The results were conflicting and neo-adjuvant radiotherapy should not be considered standard.
  - Neo-adjuvant chemotherapy has been shown to improve the 5-year survival percentage with 5% in a Cochrane review (2005), but the results could well have been biased by differing quality of preoperative staging and differing quality of the surgical procedure.

Practice point and future research opportunities
Larger studies concerning combined modality treatment are urgently needed (especially for higher tumor stages), but require a multicenter effort with a well-defined preoperative staging procedure, uniform and high quality surgery and central pathological review of the resection specimen.

Adjuvant therapy

At ASTRO 2009, Efstathiou presented the long-term outcome of 348 patients who had undergone a transurethral resection for T2-T4aNxM0 bladder cancer in the Massachusetts General Hospital (1986–2002), followed by cisplatin-based chemoradiation. The outcome was not different from retrospective data concerning curative radiotherapy, which also spares the bladder. To date, there are no phase III data, which underline the clinical benefit of adjuvant chemotherapy or chemoradiation.

- Advanced bladder cancer
  There is level I evidence for a survival benefit with use of chemotherapy with either Gemcitabine-Cisplatin or methotrexate, vincristine, doxorubicin, cisplation (MVAC). Up to now, there are no reports of a superior regimen. Neither the introduction of a newer chemotherapy combination, nor the addition of targeted agents to chemotherapy has led to a breakthrough.

Renal cancer

Active surveillance strategy

Surveillance programs for patients with increased renal cancer risk (e.g. von Hippel Lindau) need to compromise between overtreatment and under-diagnosis. In a patient with more tumors, all should be biopsied to rule out metastases. Sometimes, the computed tomography (CT) image can be misleading. This was illustrated by a benign oncocytoma, which harbored a renal carcinoma.

In case of two heavily contaminated kidneys, bilateral nephrectomy followed by dialysis is indicated. A recurrence-free interval longer than 3 years is considered long enough to enroll a patient into a transplantation program.

Neoadjuvant and adjuvant therapy

RCTs on the value of neo-adjuvant and adjuvant targeted therapy are underway. For instance, the ECOG-2805 trial randomizes patients with clear cell renal cancer between adjuvant treatment with sorafenib, sunitinib or placebo and results are expected in 2011. The EORTC-30072 trial randomizes between 3 years placebo, 1 year sorafenib/2 years placebo and 3 years sorafenib.

Targeted therapy for advanced renal cancer

- Which agent and which treatment sequence?
  - The role of cytokine therapy in future treatment appears limited. High dose IL-2 does not appear worth mentioning anymore.
  - Sunitinib is the first choice for patients with clear cell cancer and good or intermediate prognosis (according to Motzer criteria).
  - For patients with poor prognosis, an mTOR pathway inhibitor (everolimus or temsirolimus) is the first choice.

  Current research aims to sort out good responders and to point out the optimal (sequential or intermittent) order of therapies.

  Three examples were reported.
  - The tyrosine kinase inhibitor (TKI) axitinib has shown a higher in vitro affinity for the epidermal growth factor receptor (EGFR) and a phase III RCT has shown that this agent significantly improves survival compared to placebo in patients resistant to sorafenib.
  - Cediranib is a highly potent oral vascular endothelial growth factor (VEGF) signaling inhibitor, which inhibits all 3 VEGF-receptors. In a phase II placebo-controlled RCT a 34% response rate was seen (median progression-free survival 12.1 months vs. 2.8 months). The 3:1 randomization design may have lead to imbalance between the 2 groups.
  - Everolimus has been shown to improve survival in patients resistant to sorafenib.

- How should the cost benefit/ratio of new drugs be calculated?
  Health authorities struggle with the methodology used to decide whether new agents should be reimbursed. In the United Kingdom the National Institute of Health and Clinical Excellence (NICE) uses the Incremental Cost Effectiveness Ratio (ICER). The ICER is defined as Cost of new strategy minus Cost of current strategy divided by Effect of new strategy minus Effect of current strategy. The effect is depicted in Qualies. One qualy is 1 Quality-Adjusted Life Year. For adjustment a clinical utility score is being used. For instance, a 1 year-benefit and score of 0.7 translates into 0.7 qualy. The currently used utility score is the EQ-5D system, which has not been developed for cancer treatment. It does not appear sensitive enough for ICER calculation of new cancer strategies.

Practice point and future research opportunities
Health authorities and scientists should point out how future trials should be performed to provide adequate information to health economists. Apart from adequate methodology, predictive biomarkers could dramatically decrease treatment costs.

- Is nephrectomy beneficial in case of advanced renal cancer?
  Several publications claim that patients with a good response to TKI-treatment benefit from palliative nephrectomy. However it appears that there is a considerable publication bias and RCTs are ongoing. The CARMENA-trial randomizes patients with clear cell renal cancer between sunitinib only and nephrectomy followed by sunitinib. The EORTC 30073 trial randomizes patients with synchronous metastases from clear cell renal cancer between upfront nephrectomy followed by sunitinib and upfront sunitinib followed by nephrectomy.

Testicular cancer

There were two state of the art presentations by professor Alcaraz and professor Germã-Lluch. Professor Alcaraz gave a lecture on new developments concerning retroperitoneal lymph node dissection (RPLND). Professor Germã-Lluch gave an overview of important studies reported in 2009.

Laparoscopic retroperitoneal lymph node dissection (RPLND)

RPLND is used both as a component of therapy in men with early-stage germ cell tumors and for the evaluation and treatment of residual masses following systemic chemotherapy for more advanced disease. RPLND is the only reliable method to identify nodal micro-metastases and is the gold standard for pathologic staging of the retroperitoneum. The conventional approach has been the modified bilateral RPLND, but has been largely replaced by template dissections for both right- and left-sided disease. As a consequence antegrade ejaculation can be maintained in the majority of patients. Laparoscopic RPLND is an emerging technique that may reduce morbidity compared to classic RPLND. Cancer control rates appear similar, but both procedures have not been compared in RCTs.

Active surveillance for stage 1 non seminomas

In a recent analysis (Tandstad et al. J Clin Oncol 2009; 27: 2122–2128), which involved 745 patients with stage I non seminoma, the prognostic significance of vascular invasion was evaluated. With a median follow up of 4.7 years, recurrence was seen in 41.7 % of patients with tumor vascular invasion and in 13.5% of patients without invasion. In patients who had received one cycle of bleomycin-etoposide-cisplatin (BEP), these percentages were 3.2% and 1.3% respectively. Survival data are eagerly awaited.

Active surveillance encompasses up to 16 CT-scans, which increases lifetime cancer risk (Tarin et al. J Urol 2009; 181 (Issue 4):325–332). Patient compliance with the surveillance program is of utmost importance. In a recently reported study (Moynihan et al. J Clin Oncol 2009; 27: 2144–2150) 17% of patients were non-compliant. Most cases of non-compliance appeared to be caused by an unsatisfactory patient-clinician relationship.

Late complications in long-term survivors

The pulmonary function of 1, 049 long-term survivors was observed over a median period of 11.2 years (Haugnes et al. J Clin Oncol 2009; 27: 2779–2786). In 8%, restrictive lung disease was diagnosed which could be explained by factors such as bleomycin and smoking. Both high-dose cisplatin and pulmonary surgery, however, appeared to increase further the risk of restrictive lung disease.

Altena et al. recently reported the results of a study on cardiac function after cisplatin-based chemotherapy. One year after chemotherapy diastolic cardiac function was significantly poorer than before therapy initiation (Altena et al. Br J Cancer 2009; 100: 1861–1866).

Targeted therapy

In several studies microsatellite instability and BRAF mutation appear to be related with resistance to chemotherapy. The latter finding has led to the hypothesis that multi-targeted kinase inhibitors could improve the cytotoxic effect of cisplatin. Proof of concept was provided in an orthotopic model of cisplatin-sensitive and cisplatin-resistant testicular germ cell tumors synergism between sunitinib and cisplatin was found (Castillo-Avila et al. Clin Cancer Res 2009; 15: 3384–3395).

Practice point and future research opportunities
Multitargeted kinase inhibitors, such as sorafenib and sunitinib, are about to enter clinical evaluation in testicular cancer patients who receive platinum-based chemotherapy.

Epilogue

The EMUC strongly encourages close interaction between surgeons, radiotherapists and oncologists, which is pivotal for the multidisciplinary treatment of urological cancers. As Prof. Per-Anders Abrahamsson, EAU Secretary General, remarked in his welcoming speech "Not only is this multidisciplinary congress unique in its approach, it is also vital in today's world of medical subspecialization. Without this cooperation we are bound to overlook some of the many developments that take place in research, industry and training today."
Multidisciplinary teams and translational researchers should include the next EMUC meeting (Barcelona, 2011) in their schedules.

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