



## EAU 5th South Eastern European Meeting (SEEM)

### Poster Session 1: Bladder cancer and urinary diversion

Friday, 9 October 2009, 10:40–12:40

Room 1

#### S1

#### The expression of Cyclooxygenase 2 (COX-2) in myofibroblasts surrounding bladder carcinomas: from “reactive neighbourhood” to “active contributor”

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**Introduction and Objectives:** Accumulated evidence indicates that carcinogenesis is closely associated with the transformation of normal stroma into a ‘reactive’ stromal phenotype. The present study investigates the role of COX-2 – an enzyme that catalyzes the synthesis of prostaglandins – in this stromal remodeling by evaluating and comparing the expression in stromal myofibroblasts that surround normal transitional epithelium and carcinomas.

**Material and Methods:** Immunohistochemical methodology was performed on formalin-fixed, paraffin-embedded sections from urinary bladder carcinomas of 140 patients (94 males (67.1%) and 46 females (32.9%)), who underwent curative transurethral resection. The patients’ age ranged from 23 to 90 years, (mean age = 70 years). Their diagnoses were reported as follows: Grade I n = 27 (19.3%), Grade II n = 30 (21.4%), and Grade III n = 54 (38.6%). 29 (20.7%) cases of normal bladder epithelium were selected from patients that underwent diagnostic biopsies. Monoclonal antibody against the human Cox-2 molecule was used. A molecular profile was created for each patient and the induction or downregulation of Cox-2 expression was evaluated and documented. Relationship between Cox-2 and grades of carcinogenesis were evaluated by Spearman’s rank correlation coefficient and validated by Fisher’s exact test.

**Results:** Myofibroblasts surrounding normal epithelium showed no cytoplasmic immunoreactivity in 41.4%, and only 6.9% overexpressed this enzyme. 63% of myofibroblasts surrounding carcinomas presented with moderate and strong immunoreactivity, and only 12.6% had no staining. The Spearman rank correlation coefficient (rs) revealed a positive correlation (r = 0.29, p-value = 0.001), meaning that COX-2 is overexpressed in myofibroblasts surrounding bladder carcinomas. Furthermore positive correlation has been revealed when Spearman rank correlation coefficient (rs) performed for Grades of carcinogenesis (normal–Grade I, r = 0.30, p-value = 0.026, Grade I–Grade II, r = 0.31, p-value = 0.018, Grade II–Grade III, r = 0.38, p-value < 0.001).

**Conclusions:** COX-2 expression is upregulated in stromal myofibroblasts surrounding bladder carcinomas compared to normal transitional epithelium. This study emphasizes that the role of COX-2, which is important molecular target of chemoprevention, is not only confined to the tumor epithelial cells but is also extended in the stroma especially in the stromal myofibroblasts, which are important players in the process of bladder carcinogenesis.

#### S2

#### Evaluation of the clinical value of urinary NMP22 as a marker in the surveillance of superficial transitional cell carcinoma of the urinary bladder

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**Introduction and Objectives:** To prospectively evaluate the clinical role of urinary NMP22 as a marker for transitional cell carcinoma of the urinary bladder in surveillance settings.

**Material and Methods:** Single voided specimens were obtained from 25 consecutive patients who presented for cystoscopy. All of these patients presented with previously treated superficial bladder TCC with or without haematuria or irritative symptoms for regular follow up. The urine sample was used for urine microscopy, and for measuring NMP22 levels in 12 to 36 months of follow up.

**Results:** Bladder tumours were found in 5 of 25 (20%) patients on surveillance. The NMP22 levels were significantly lower in patients with lower stage (Ta vs. T1–3), low grade (G1, G2 vs. G3, CIS) and papillary morphology. The optimum threshold for NMP22 was 10.0 U/ml, providing a sensitivity, specificity, positive predictive value and negative predictive value of 40.0, 85, 38.5 and 88.0% respectively. Sensitivity and specificity were better in patients being on surveillance for a longer period and with sterile urine samples.

**Conclusions:** Urinary NMP22 levels are significantly higher in patients with bladder tumour than in those negative for tumours, and test predictability improves with increasing stage and grade. The overall sensitivity for urinary NMP22 is similar to cystoscopy but can not replace it. With cystoscopy together gives almost 100% accurate diagnosis of relapsing bladder TCC. Our study suggests that the clinical role of urinary NMP22 as a diagnostic marker can be at best supportive only, with potential advantage in follow up after resection of high risk bladder TCC (T1G3, CIS).

#### S3

#### Urine IL8 concentration correlates with advanced bladder tumors

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**Introduction and Objectives:** High prevalence of bladder carcinoma together with recurrence tendency represent

important medical problem in spite of successful early treatment procedures. Local tumor grows as well as metastatic potential is critically dependent of microenvironmental growth factor production. Several chemokines were pointed as important in TCC pathogenesis. On the other side, local specific antitumor immune response represents most important factor that influence tumor growth and spreading and finally disease outcome. Therefore, urine cytokine levels could be valuable indicators of both tumor aggressivity and local immune response effectiveness. Our aim was to investigate urine cytokine levels in patients with TCC correlating them to clinical and pathological signs of tumor advances.

**Material and Methods:** Naturally micturated urine samples were obtained from 40 patients with newly diagnosed bladder cancer. Patients were divided according to cytological, radiological and pathohistological findings in group with less (G2, pT1) or more aggressive TCC (G3-G4, pT2-pT3). Concentration of cytokines (IL1b, TNFa, IFNg, IL2, IL4, IL5, IL6, IL8, IL10, IL12) was estimated with commercial flowcytometric test kit.

**Results:** Levels of IL2, T lymphocyte activating cytokine, together with IL12 were significantly higher in urine samples from patients with more aggressive TCC. IL6 concentration was higher in group with advanced TCC. Most striking finding was significant elevation of TH2 cytokines IL4 and IL5, together with IL8, that reached almost 10 times more concentrations in urine samples from patients with more aggressive TCC (IL4 = 2279±270 vs 139±133 pg, IL5 = 2498±118 vs 54±50 pg, IL8 = 1863±533 vs 271±197 pg, respectively). Levels of IFNg, IL1b, IL10 and TNFa did not differ between two groups.

**Conclusions:** Our study results indicate that more aggressive bladder tumor forms are associated with local TH2 immune response, together with high IL8 chemokine levels.

#### S4

##### Chronic inflammation and bladder cancer: How hot is the link?

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**Introduction and Objectives:** Nuclear Factor  $\kappa$ -B (NF $\kappa$ B) is the 'supervisor' protein of chronic inflammation and malignant transformation. NF $\kappa$ B remains in the cytoplasm transcriptionally silent. Activation of NF $\kappa$ B in response to extracellular stimuli lead to translocation to the nucleus and activation of transcription of a plethora of genes, involved in tumor promotion and proliferation. Our objective was to evaluate the expression of NF $\kappa$ B in Transitional Cell Carcinoma of the bladder and its correlation with histological Grade and clinicopathological parameters.

**Material and Methods:** Immunohistochemical methodology was performed on formalin-fixed, paraffin-embedded sections from urinary bladder carcinomas of 140 patients (94 males (67.1%) and 46 females (32.9%)), who underwent curative transurethral resection. The patients' age ranged from 23 to 90 years, (mean age = 70 years). Their diagnoses were reported as follows: Grade I n = 27 (19.3%), Grade II n = 30 (21.4%), and Grade III n = 54 (38.6%). 29 (20.7%) cases of normal bladder epithelium were selected from patients that underwent diagnostic biopsies. Monoclonal antibody against NF $\kappa$ B was used. A molecular profile was created for each patient and the induction or downregulation of nuclear and cytoplasmic NF $\kappa$ B expression was evaluated and documented. Relationship between NF $\kappa$ B and Grades of carcinogenesis were evaluated by

Spearman's rank correlation coefficient and validated by Fisher's exact test.

**Results:** NF $\kappa$ B signal was both cytoplasmic and nuclear. NF $\kappa$ B cytoplasmic expression was undetectable in 6.9% (2/29) of specimens of normal epithelium and overexpressed in 38.9% (7/29). On the other hand, none of the well differentiated tumors and only 3.3% (1/30) of moderate and 1.8% (1/54) of poor differentiated carcinomas showed negative NF $\kappa$ B cytoplasmic staining. Statistical analysis revealed a negative correlation between cytoplasmic molecular expression and grades of differentiation. As normal cells progressively gained atypical characteristics the cytoplasmic expression of NF $\kappa$ B has been downregulated. As far as nuclear staining of NF $\kappa$ B is concerned, 100% (29/29) of normal transitional epithelium lacked nuclear staining. Only in 13% (7/54) of poorly differentiated carcinomas there was no nuclear staining and 26% (14/54) of them showed strong immunoreactivity. Statistical analysis revealed a strong positive association between histological grade and nuclear expression of NF $\kappa$ B (test of trend p-value <0.001). No association with age or gender was observed.

**Conclusions:** Our results indicate an induction of this key molecule along the carcinogenesis path and the level of differentiation. Although inflammation has long been known as a localized protective reaction of tissue, there has been a new realization about its role in cancer. These observations imply that anti-inflammatory agents that suppress NF $\kappa$ B should have a potential role in bladder cancer chemoprevention.

#### S5

##### Primary adenocarcinoma of the urinary bladder.

##### Presentation of 5 cases

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**Introduction and Objectives:** Adenocarcinomas of urinary bladder is a rare type of neoplasm and account for 0.5–2 % of all urinary bladder cancers. They can be primary or those arising from urachus. Histologically, adenocarcinomas are mucus secreting and may have glandular, colloid, signet-ring, hepatoid or mixed patterns.

**Material and Methods:** 5 patients were diagnosed as primary urinary bladder adenocarcinomas within the last 4 years in the G.h.of Korinthos.

**Results:** 3 of all patients were 54–85 years old males, with medium grade primary bladder adenocarcinomas which were infiltrating the muscular bladder wall. The rest 2 cases concerned 73 and 76 female patients with low grade muscle infiltrating primary bladder adenocarcinoma. Immunohistochemical examination followed and confirmed the diagnosis demonstrating: CK7 (+), CK20 (+), CK 34 $\beta$ E12 (+), CEA (+), PSA (-), PSAP (-), Vimentin (-). All patients were presented with intermittent macroscopic hematuria, which was accompanied by symptoms of vesical irritability (frequency, urgency and dysuria) in 4 of them. All patients underwent initially transurethral resection of bladder tumour which was followed by radical cystectomy in 3 of them. In 2 patients identified sites of metastasis at the time of diagnosis.

**Conclusions:** Primary adenocarcinomas of urinary bladder are quite rare compared to all other types of bladder cancers. They are often localized at the time of diagnosis, but muscle invasion is usually present. Prognosis is poor and 5 year survival is usually less than 40%, despite of aggressive surgical intervention.