Debates on Bladder Cancer

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Highlights Bladder Cancer AUA 2010

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Abstract
At this year annual meeting in San Francisco, one of the main focuses was on bladder cancer preclinical studies, diagnostics and prognostic factors.

Key words: bladder cancer, AUA annual meeting San Francisco 2010, prognostic factors

BASIC RESEARCH

Nakanishi et al. (#776) evaluated the impact of gene deletion of membrane-associated prostaglandin synthase-1 (mPGES-1), the terminal synthase in the generation of PGE2, in the BBN mouse model. Two month old male C57Bl/6 mice with global homozygous deletion for Ptges (mPGES-1 KO) and wild-type (WT) were treated with and without BBN in drinking water (n=5/grp) for 23 weeks. Bladders were harvested, weighed, fixed, step sectioned and evaluated by H&E for pathologic stage and grade and percent involvement of tissue by tumor. Urine was collected prior to sacrifice and evaluated for PGE-2 metabolites (PGEM) by ELISA. WT bladders were significantly heavier than KO bladders (mean 0.18 vs. 0.04 g respectively; p=0.03). Four of 5 WT mice had pT3 and one pT2 disease. Three of 5 KO mice had pT1 and 2 had pT2 disease. The tissue involvement was significantly less in the KO animals as well (54 vs. 87%, p=0.03). Pathologic stage was dependent. Urine metabolites were reduced 50% in the KO compared to WT animals (mean 18.9 vs. 45.2 pg/ml respectively; p<0.01). Genetic deletion of mPGES-1 resulted in significant decreases in PGE-2 as evidenced by lower urinary PGEM and in pathologic stage and percent tissue involvement by tumor. Stage distribution was dependent on genotype. Increased bladder weights in the WT mice compared to KO mice were directly related to the increased tumor burden. Taken together, these results suggest that inhibitors of mPGES-1 may prove to be an alternative to COX inhibition and possibly prove useful in the management of high-grade bladder cancer.

Oncolytic herpes simplex viruses replicate selectively in cancer cells and are promising therapeutic agents for cancer. G47delta, a triple-mutated herpes simplex virus type 1 (HSV-1) with deletions in the gamma34.5 gene and the alpha47 gene and with inactivation of the ICP6 gene, exhibits high replication capabilities in tumor cells while preserving the safety. **Fukuhara et al. (#778)** developed an

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armed oncolytic HSV-1 generation system that allowed insertion of desired transgenes into the ICP6 locus of the G47delta backbone. Using this system, they generated T-mflL12 that expresses fusion-type murine interleukin 12 (IL-12) and T-01, a control vector. Human bladder cancer lines RT4, T-24, SW800, EJ-1 and JON and murine bladder cancer lines MB49 and MBT-2 were used for in vitro evaluation. In C57BL/6 mice with subcutaneous murine MB49 tumors, mock, T-01 or T-mflL12 was inoculated intraneoplastically and tumor size measured. In a lung metastases model, C57BL/6 mice received intravenous injections of MB49 cells, and viruses were repeatedly administered into the tail veins. In all cell lines studied, T-01 and T-mflL12 showed comparable cytopathic activities. In MB49 subcutaneous tumor model, both T-01 and T-mflL12 caused significant inhibition of tumor growth compared with mock. Furthermore, T-mflL12 was significantly more efficacious than T-01. In MB49 lung metastases model, intravenous administration of T-01 or T-mflL12 significantly prolonged the survival compared with mock treatment. T-mflL12 was more efficacious than T-01, especially at lower doses. The authors conclude that oncolytic HSV-1 therapy can be a potent therapeutic approach for bladder cancer. Especially for lung metastases, intravenous administration may be a useful delivery route of oncolytic HSV-1. Moreover, antitumor efficacy of oncolytic HSV-1 can be augmented by expression of immunostimulatory transgenes such as IL-12.

Verma et al. (# 1153) investigated the effect of Mytomycin C (MMC) on levels of vascular endothelial growth factor and its receptors in bladder cancer cells and in bladders of rats intravesically instilled with MMC. They hypothesized that MMC increases the angiogenic potential of both cancer and normal cells. One day after MMC treatment (6-100 µg/ml), they measured proliferation, and VEGF-A, VEGFR-1 and VEGFR-2 levels in T-24 and RT4 bladder cancer cells. The effect of pretreatment of VEGF siRNA on MMC induced decreases in proliferation was measured. Rats were intravesically instilled with saline or MMC (200 µg/rat). Urinary VEGF levels and bladder levels of VEGFR-2 protein relative to actin and VEGF, VEGFR-1, and VEGFR-2 mRNA relative to GAPDH mRNA were measured. Although MMC treatment inhibited cell proliferation, it did not decrease VEGF protein expression in T-24 and RT4 cells. In fact, in T-24 cells, MMC (6-50 µg/ml) increased VEGF mRNA expression normalized to GAPDH 3-13 fold and increased VEGFR-2 mRNA and protein expression, 2-12 fold and 2-5 fold, respectively. Levels of VEGFR-1 were unchanged. In T-24 cells, MMC (25 µg/ml) reduced proliferation 40 ± 5%, while increasing VEGF mRNA levels 3.4 fold. However, pretreatment of MMC treated cells with VEGF siRNA blocked VEGF mRNA production and potentiated MMC induced reductions in proliferation by an additional 27 ± 4%. Similar results were seen with RT-4 cells. In rats intravesically instilled with MMC, urinary VEGF/creatinine was increased 80% and VEGFR-2 mRNA and protein levels were increased 80% and 150%, respectively, compared to levels in saline instilled rats (n = 4-6). MMC treatment increased levels of VEGF mRNA and VEGFR-2 mRNA and protein in bladder cancer cells. VEGF siRNA potentiated mitomycin inhibitory effects on proliferation in bladder cancer cells. Intravesical instillation of MMC increases urinary VEGF and bladder VEGFR-2 levels. Taken together, these results suggest that MMC increases the angiogenic potential of both cancer and normal cells. Combining MMC with agents that reduce VEGF levels may be of value in the treatment of urothelial carcinoma.

Gust et al. (# 774) investigated the Notch pathway which plays a critical role in growth and differentiation. Thirteen bladder cancer cell lines were screened for Notch-1 and Notch-2 expression by Western blot and real-time PCR. Immunohistochemistry was performed in 152 bladder cancer patients. Alterations in gene expression after Notch-2 silencing with siRNA were measured by expression microarray in 3 cell lines. Wound healing assays were performed after treatment

with Notch-2 siRNA versus scrambled siRNA. Epithelial cell lines with low invasive potential expressed Notch-1 at high and Notch-2 at low relative levels. Highly invasive, mesenchymal cell lines expressed high levels of Notch-2 and low levels of Notch-1. Microarray analysis revealed altered expression of genes related to epithelial to mesenchymal transition, protein and endosome trafficking, and cell-cell connections, when Notch-2 was silenced with siRNA. Notch-2 silencing decreased the migration of UC3 cells in the wound-healing assay. These data suggest that Notch signaling is a promising target for therapy in bladder cancer.

Yoon et al. (# 971) explored synergistic anti-tumor effect of cisplatin and novel dual PI3K/mTOR inhibitor NVP-BEZ235 against T24R2 cell and related death receptor signaling. The cisplatin resistant invasive human bladder cancer cell line T24R2 was treated with various dose-combinations of cisplatin (5-15ug/ml) and NVP-BEZ235 (0.3-20uM) and cell viability was assessed with CCK-8 assay. C-FLIP, caspase 3, 8, 9, p-Akt and t-Akt expression was evaluated with immunoblotting and flow cytometric cell cycle analysis was performed. Suppression of death receptor signaling in T24R2 was evaluated by dose-response study with TRAIL. T24R2 showed significantly higher c-FLIP expression compared to other chemo-naive human bladder cancer cell lines (HTB5, HTB9, J82, SW1710, UMUC14, 253J, T24) and unlike other cell lines, c-FLIP expression in T24R2 was not suppressed by cisplatin only. Treatment with TRAIL markedly suppressed T24 proliferation while there was virtually no change in T24R2 proliferation by TRAIL treatment. NVP-BEZ235 single treatment did not cause any changes in c-FLIP expression in T24R2. On the contrary, combined treatment with NVP-BEZ235 and cisplatin completely abrogated c-FLIP expression in T24R2 and potentiated anti-tumor effect of each drug up to 80%. Combined treatment also activated caspase 3, 8, and 9 in T24R2 and suppressed p-Akt / t-Akt, resulting in significant increase in the sub-G1 apoptotic cell population. These results show that cisplatin resistance in T24R2 cell is closely related with c-FLIP expression and suppression of death receptor signaling, which can be reversed by combined treatment with NVP-BEZ235. Further research is necessary to test NVP-BEZ235 as a new combinational-targeted therapeutic agent to overcome cisplatin resistance in human bladder cancer cells.

PROGNOSIS

Ploeg et al. (#1719) evaluated the impact of time from definitive therapy to recurrence with clinical outcomes. 1,409 patients from the Netherlands with muscle-invasive bladder cancer were included in this study. All patients underwent either radical cystectomy or radiation therapy with curative intent from 1989-2005. Of the 1,409 patients, 330 (23%) experienced disease recurrence. The median survival for those who had a recurrence was 4 months. 1 and 3 year survival after a subsequent recurrence was 22% and 9% respectively. On multivariable analysis, location of and treatment for recurrence were independent predictors of survival in patients who underwent cystectomy. Age at diagnosis of disease recurrence, location, and treatment for recurrence were independent predictors of survival for patients who underwent radiation therapy. The authors conclude that time to recurrence had no prognostic value in this study. Time from initial therapy to recurrence does not appear to impact survival of cystectomy patients. Patients who were treated after disease recurrence, regardless of initial treatment choice, did better than those who were not treated. While this could be a selection bias for lower tumor burden and healthier patients, there is a signal that even recurrences are heterogeneous in their biological and clinical behaviour. Larger datasets with more homogenous populations would allow to refine the management of patients with bladder cancer after definitive treatment.

BIOMARKERS

In a study of 315 patients treated with radical cystectomy, **Youssef et al. (#1155)** found a significant difference in tumor stage, grade, and architecture and COX-2 alterations between patients with bilharzial related bladder cancer and those with non-bilharzial related bladder cancer ($p<0.05$). Bilharzial related bladder cancer presented with lower grade, higher stage, and non-papillary non-urothelial carcinoma. COX-2 overexpression was associated with pathological T stage, grade and lymphovascular invasion. COX-2 expression was an independent predictor of disease recurrence and cancer specific mortality only in bilharzial related bladder cancer but not in non-bilharzial related bladder cancer. Taken together, these findings suggest that COX-2 may be a good prognostic marker especially in inflammatory cancers like in bilharzial related bladder cancer. Further research should focus on the evaluation of COX-2 as well as COX-2-targeted prevention or therapies in bilharzial related bladder cancer.

Kauffman et al. (# 162) evaluated bladder cancer cells for BCG receptors to investigate why BCG can kill bladder cancer cells in the absence of immune cells. Traditionally, BCG is presumed to treat bladder cancer cells via stimulation of the immune system. However, there are toll-like receptors (TLR) 2 and 4 that are known receptors for BCG. These receptors are believed to be restricted to immune cells. The authors evaluated bladder cancer cells for the presence of TLR using a tissue microarray constructed from 41 patients subsequently treated with 6-course BCG. TLR2 and 4 was expressed in 7 bladder cancer cell lines with RTPCR techniques. Of the 41 patients, 20 were BCG-responsive and 21 were BCG-nonresponsive. TLR2 and TLR4 proteins both stained positive in most (>70%) bladder cancer specimens, with no significant correlation to cancer stage or grade. For TLR2, the mean %-tissue positivity score was significantly higher in BCG responsive tumors relative to BCG non-responsive tumors (1.8 vs. 1.0, $p=0.027$). Furthermore, TLR2 was expressed at some level in all BCG responsive tumor specimens compared to fewer than half (10/21) of BCG non-responsive tumors ($p<0.001$). Similarly, for TLR4, absent expression was nearly twice as common in the BCG-NR group, which had a lower mean %-tissue positivity score (1.0 vs. 1.3) and lower mean staining intensity score (0.65 vs. 0.80) than the BCG-R group, however these findings were not statistically significant ($p=0.31$, 0.30, respectively). Consistent with the immunohistochemistry data, TLR2 and TLR4 RNA transcripts were each detected in the majority of bladder cancer cell lines. The authors suggest that this study demonstrates that immune-cell BCG receptors, TLR2 and TLR4, are present in bladder cancer cells and may be potential markers for BCG sensitivity. This is an exciting avenue for further research.

Matsumura et al. (#161) studied the expression of the molecular transporter human equilibrative nucleoside transporter (hENT) that is necessary for gemcitabine transportation into the cells of tumors. The authors hypothesized that the expression level of hENT1 can predict survival in advanced bladder cancer treated by gemcitabine-based chemotherapy. 40 patients with advanced bladder cancer treated by GC (gemcitabine+cisplatin) regimen (17 patients) and GCT (GC+paclitaxel) regimen (23 patients) were evaluated. They studied the expression level of hENT1 by immunohistochemical staining of formalin-fixed, paraffin-embedded bladder cancer tissues. Of the 40 tissue samples, 20 samples revealed hENT1 high and low expression. Patients with hENT1 low expression had a median overall survival of 11.6 months from initiation of gemcitabine based chemotherapy. In contrast, patients with hENT1 high expression had a median survival of 17.3 months. Kaplan-Meier analysis revealed that patients who had low hENT1, were at significantly higher risk of death compared to patients with high hENT1 expression ($p=0.0026$). Moreover, in a multivariable analysis that adjusted for effects of extent of metastases only hENT1 expression was an independent predictor ($p=0.003$) of survival.

The authors concluded that patients with high levels of hENT1 in their bladder cancer have significantly better overall survival than those with low expression. Immunohistochemical evaluation of hENT1 expression can be a promising biomarker for the prediction of clinical response and the prognosis of patients with advanced bladder cancer treated by gemcitabine-based chemotherapy. Validation in a larger cohort is necessary and establishment of set criteria for low as well as high expression is necessary.

Angiogenesis is critical to tumor growth by providing growth factor milieu including nutrients, oxygen, and extracellular structure to the tumor. Vascular endothelial growth factor (VEGF), fibroblast growth factor (BFGF), thrombospondin 1 (TSP-1) levels and microvessel density (MVD-CD31) have prognostic value in urothelial cancer in small studies. **Shariat et al. (#1032)** evaluated 204 radical cystectomy specimens with urothelial cancer for expression of the above named angiogenesis molecular markers and correlated this expression with cell cycle- (Cyclin E1, Cyclin D1, p53, p21, p27, pRB), proliferation- (Ki-67), and apoptosis-related (caspase-3, survivin and Bcl-2) molecular markers. All four angiogenesis markers were associated with established clinicopathologic features of aggressive bladder urothelial carcinoma such as stage, lymphovascular invasion, and lymph node metastasis and other molecular markers. After adjusting for the effects stage and grade of the tumor, BFGF and TSP-1 were independent predictors of disease recurrence (HR 3.6, p=0.002 and HR=2.2, p=0.001, respectively) and cancer specific mortality (HR 2.8, p=0.02 and HR=2.3, p=0.003, respectively). When all four angiogenesis markers were included in the multivariable model, BFGF and TSP-1 retained their independent association with disease recurrence (HR=2.9, p=0.014 and HR=1.8, p=0.022, respectively) but only TSP-1 was independently associated with cancer specific mortality (HR=1.9, p=0.031). The authors concluded that angiogenesis molecular markers are altered in urothelial carcinoma and are associated with outcomes of radical cystectomy. In this initial study VEGF was commonly altered in UCB specimens, thereby serving as a possible target for therapy. Down-regulation of TSP-1 and up-regulation of BFGF are independent predictors of bladder cancer recurrence, and down-regulation of TSP-1 is also associated with bladder cancer specific mortality. The integrated understanding of the biology of angiogenesis related molecules in bladder cancer and its translational relevance may lead to the development of novel treatment approaches for this disease.

Schultz et al. (# 160) evaluated tissue microarrays of urothelial cancers for alterations in the mTOR pathway to identify prognostic markers. The mTOR pathway is critical in cell proliferation, angiogenesis, and cell migration. The tissue microarray included 144 radical cystectomies (14 pTis/pTa, 16 pT1, and 114 pT2-4 cases). On univariate analysis, PTEN, c-MYC, p27, phos Akt, phos S6 had lower expression in invasive urothelial carcinoma compared to benign urothelium. C-MYC, p27, and phos Akt expression significantly correlated with divergent aggressive cellular differentiation (sarcomatoid, squamous, and adenocarcinoma) and presence of invasion. Phos S6 was predictive of overall survival (p=0.01), disease-free survival (p=0.008) and progression (p=0.05) with higher expression levels predicting favorable outcome. On multivariable analysis phos S6 remained an independent predictor of disease-free survival (p=0.006) after adjusting for the effects of clinical stage, pathologic stage, invasive tissue microarray spot histology and divergent aggressive differentiation. The authors conclude that there is an overall downregulation of mTOR pathway members in advanced bladder cancers. Phos S6 was an independent predictor of disease-free survival on univariate and multivariate analysis. Further validation of these findings is necessary in larger advanced cohorts.

Understaging of bladder cancer occurs in 50% of patients resulting in non-appropriate care. Additionally, understanding the biological aggressiveness of the cancer is critical to

counsel patients regarding the need for systemic therapy. Several investigators have evaluated biomarkers that individually have minimal additive benefit in predicting the biological potential of a cancer, but collectively may improve the predictive accuracy. **Youssef et al. (#1021)** prospectively assessed the predictive value of a panel of biomarkers (cyclin E1, p53, p21, p27 and pRB/Ki-67) for staging of patients with urothelial carcinoma of the bladder (UCB). 174 consecutive patients treated with transurethral resection (TUR) and/or radical cystectomy (RC) for UCB were prospectively included in the study starting in January 2007. A prognostic score (PS; favorable = 2 or less altered biomarkers; unfavorable = more than 2 altered biomarkers) was defined and correlated with clinical and pathological data. The study comprised of 102 RC patients and 72 TUR cases. Unfavorable PS was noted in 36.3% of RC cases and 16.6% of TUR cases. In RC patients, an unfavorable PS was significantly associated with advanced tumor stage (p=0.02), the presence of lymphovascular invasion (p=0.017) and disease recurrence (p=0.04). In the subgroup of patients who had biomarker evaluation at TUR and then underwent RC (n=32), 75% and 50% of the cases with unfavorable PS showed upstaging and LN involvement at RC versus 29% and 12.5% in cases with favorable PS. Unfavorable PS at TUR was associated with upstaging (p=0.022), lymphovascular invasion (p=0.001), LN metastasis (p=0.026) and recurrence (p=0.014). The preliminary analysis of this prospective trial strongly suggests that a panel of five biomarkers not only predicts poor outcome after RC but also improves the identification of patients at risk of upstaging at RC. An unfavorable prognostic score may identify patients who are most likely to benefit from neo-adjuvant and adjuvant chemotherapy. These findings need multicenter validation before wide application.

Lerner et al. (# 1715) A prospective multi-institutional clinical trial was conducted to test the hypothesis that p53 is prognostic and predictive in patients with pathologically organ-confined bladder cancer following radical cystectomy. The secondary objective was to evaluate cell cycle regulatory proteins p21, Rb, p16, p27 and their role in clinical outcomes. Patients with pT1-2N0M0 bladder carcinoma following radical cystectomy and bilateral pelvic lymph node dissection were eligible. Entry criteria required ≥ 15 dissected nodes or a post-operative abdominopelvic CT for patients with < 15 nodes. Immunohistochemistry was performed on representative TUR or cystectomy tumor specimens. As adjuvant chemotherapy did not impact recurrence free survival or overall survival, all patients were included regardless of adjuvant therapy. 499 eligible patients from 43 sites in US, Canada and Europe were registered between 8/97 and 1/06. Lymphovascular invasion was associated with decreased recurrence free survival and overall survival, and patient age was associated with overall survival. No single biomarker was associated with recurrence free survival or overall survival. However, the combined variables p53/p21, p53/p21/Rb, or 5 markers in combination were not associated with recurrence free survival or overall survival. These findings are in contradiction to a large body of evidence regarding the predictive/prognostic value of these markers.

Rhijn et al. (#1714) evaluated tumor sub-stage, clinicopathologic parameters, and 4 molecular markers with regard to clinical outcomes in patients with pT1 urothelial carcinoma treated with BCG. Tumors were sub-staged into micro-invasive and extensive-invasive and also by invasion of the muscularis mucosae. Multivariable analysis was carried out for recurrence and progression with clinical, pathologic and molecular markers (FGFR3 mutation, MIB-1, p53, p27) as variables. European Organisation for Research and Treatment of Cancer (EORTC) risk-scores were also calculated. Actual progression was observed in 20% of patients. In multivariable analysis for recurrence, tumor multiplicity was the only significant variable (HR: 2.0, 95% CI: 1.4-3.0, p<0.001). In multivariable analysis for progression, female gender (HR: 2.7, 95% CI 1.3-5.8, p=0.014), sub-stage (HR: 2.8; 95%CI 1.5-5.7, p=0.003)

and CIS (HR: 2.1, 95% CI: 1.2-4.0, p=0.015) were all significant predictors. Molecular markers did not appear to add significant benefit for prediction of recurrence and progression in this study. Additionally, the value of the EORTC risk score was also limited. The authors conclude that clinico-pathologic features at this point remain the most robust predictors of recurrence and progression in this heterogenous patient population.

CLINICAL NON MUSCLE-INVASIVE

Alkhateeb et al. (#160) As men and women age, their bladder wall thicknesses markedly change. Men develop a thicker bladder due to prostatic obstruction and women develop a thinner bladder, particularly after menopause. Proper sampling of detrusor muscle is essential for accurate pathological diagnosis. There is a general belief among urologists that females are at a higher risk for absence of detrusor muscle due to a perceived danger of increased risk of bladder perforation. The authors evaluated patients undergoing a TURBT between 1990 and 2009 for the presence of muscle in the biopsy specimen. A total of 921 patients with primary non muscle-invasive bladder cancer were included. Male to female ratio was 3.2:1, mean age was 65.9 years, pathological stage distribution was pTa in 55.7%, ≥ pT1 in 41.8% and pTis in 2.5% and detrusor muscle was present in 515 patients (63.2%). In a multivariable model, independent predictors for the presence of detrusor muscle were age ≥65 years (OR 1.48, 95% CI 1.10-1.99, p=0.02), pT1 tumors (OR 12.34, 95% CI 4.31-35.2, p=0.001), grade 3 tumors (OR 1.68, 95% CI 0.39-0.89, p=0.01), tumors ≥ 3cm in size (OR 3.2, 2.18-4.68, p=0.001), multifocality (OR 1.60, 95% CI 1.18-2.18, p=0.002) and concomitant CIS (OR 1.83, 95% CI 1.12-2.98, p=0.01). Gender did not predict for the presence of detrusor muscle (OR 1.21, 95% CI 0.86-1.71, p=0.26). The authors conclude that females are not at higher risk for absence of detrusor muscle in the first TURBT. However, younger patients and those with small and single tumors are at risk for not having detrusor muscle in the pathological specimen. Every effort should be made for proper sampling of detrusor muscle in order to have an accurate pathological diagnosis in order to administer risk-adjusted management.

Matsumoto et al. (# 1465) analyzed the association between clinicopathologic parameters and late recurrence and progression in non muscle-invasive bladder cancer. 248 patients who were classified as BCG failures comprised this cohort (43 BCG refractory and 205 BCG relapses). BCG refractory patients were found to be independently at risk for stage progression (HR 4.31, p<0.001). The 5 and 10 year progression free survival rates were 54.6% and in 26.1% in refractory patients, compared to 82.9% and 80.1% in relapsing patients (p<0.001). The authors concluded that early cystectomy should be considered for BCG refractory patients as progression rates are high in this cohort. The same group from Japan **(# 1357)** addressed the issue of late recurrence and progression in non muscle-invasive lesions after a five-year tumor-free period. From a cohort of 1,314 patients treated between 1985 and 2004, 361 were identified with a 5-year disease free interval. The recurrence free rates were 82.8% and 76.3% at 5 and 10 years. There was no significant difference in the recurrence rates among the risk groups. Mitomycin C was associated with delayed recurrence. The authors conclude that low-risk lesions may not require continued observation after a 10-year non-recurrence, patients may have progression after 5 years and require observation.

Zhangqun et al. (#1355) reported on a prospective multicenter trial of white light cystoscopy (WL) versus narrow band (NB) imaging in the detection of non muscle-invasive bladder cancer. 103 patients were studied in 4 academic centers. Bladders were

mapped by both modalities and a biopsy was taken from an area felt to be normal under both conditions. The operational characteristics of both techniques were then evaluated. 87 patients demonstrated 167 confirmed tumors. 41 tumors were detected by NB only while 6 lesions were detected by WL only. The detection rate of NB was 96.4% versus 75.4% for WL ($p<0.0001$). The false positive rates were 39.1 for NB and 41.4 for WL and the positive predictive value was 75.6% and 69.6%, respectively. The negative predictive value was 93.1 for NB and 65.5 for WL. These data suggest that narrow band imaging may confer superior detection of non muscle-invasive tumors than white light cystoscopy. The clinical significance of these tumors remains to be proven.

Hemani et al. (# 1354) reported on the impact of office-based endoscopic surgery on disease recurrence. 379 TUR cases were performed in total with 210 done in the office. Office transurethral resection (TUR) was associated with a significantly higher likelihood and shorter interval to recurrence when compared to hospital TUR [HR 1.42 (1.09-1.85) 95% CI]. The median time to recurrence was 6 months in the office-based cohort compared to 12.9 months for the hospital using similar surveillance schedules. While it is likely that this may reflect inadequacy of office-based resection, other biases have to be considered. Wrong patient selection could account for the difference for example.

Di Stasi et al. (#1346) studied the efficacy of immediate pre-transurethral resection electromotive EMDA MMC with post-transurethral passive diffusion (PD) MMC instillation or transurethral resection alone in patients with non muscle-invasive bladder cancer. Over a 10-year period, 352 patients were randomized to one of the three arms described above. In the post-TUR group 40mg of MMC was administered immediately after TUR for 60 minutes. In the EMDA arm 40 mg of MMC was given with 20mA electric current for 30 minutes. Primary endpoints for this study were recurrence and disease specific survival. Median follow up was 85.4 months over which 188 (53%) patients experienced disease recurrence. 63.8%, 58,8% and 37.6% of patients experienced disease recurrence in the TUR alone, PD/MMC group and EMDA/MMC group, respectively. Overall median disease-free interval was 12.9, 16.4 and 56.9 months in the TUR alone, PD/MMC group and the EMDA/MMC group respectively ($p<0.001$). 36% of patients in the post-TUR group reported bladder symptoms and 24% discontinued treatment because of pain or spasms; interestingly there were no side effects reported in the EMDA/MMC pre-TUR group. EMDA/MMC decreased the risk of recurrences in patients with high and intermediate risk non muscle-invasive bladder cancer and appeared to be well tolerated. Current multicenter trials are ongoing.

Many articles have suggested that higher volume surgeons who practice at high-volume centers have better outcomes. Accurate surrogates for quality are difficult to define. It has been suggested that the presence of detrusor muscle (DM) in the first transurethral resection of bladder tumor (TURBT) may serve as a surrogate for complete/adequate resection in non muscle-invasive bladder cancer. Between 1990 and 2009, **Alkhateeb et al. (#1022)** identified all TURBT procedures performed at a single institution for bladder cancer and the surgeons performing them. They determined the mean number of TURBTs preformed per surgeon per year and then developed tertiles of surgeons: low, moderate and high based on their volume (<6, 6-12 and >12 procedures per year, respectively). Clinical and pathological variables assessed included: age and gender, tumor size and multifocality, pathological tumor stage and grade, concomitant carcinoma in situ (CIS) and weather DM was sampled. They limited their analysis to patients' initial TURBT and compared the outcome (presence of DM) between the three tertiles using univariate analysis and multivariable logistic regression adjusting for the clinical and pathological variables. The mean number of TURBTs performed was 14.9 procedures (median 15.1) per surgeon per year. Among the 624 patients

included, the overall rate of DM sampling was 54.0%. There was a significant increase in the rate of DM sampling with time 36.6% vs. 45.8% vs. 62.8% for the 1st, 2nd and 3rd 7-year periods (p<0.001). When comparing volume tertiles, the DM sampling rate was 47.8 % in the low-volume group compared to 53.6% in the moderate-volume group (OR 1.57, 95% CI 0.98-2-49, p=0.056) and 58.2% in the high-volume group (OR 1.71, 95% CI 1.05-2.77, p=0.029). The authors showed a volume-outcome relationship in TURBT with a significant correlation between surgeon volume and the presence of DM in the initial resection. This could be used to assess quality of the TURBT, but extenuating circumstances such as size and location of the tumor, patient characteristics like previous bladder surgery and body habitus must be considered when interpreting if the lack of muscle in the TURBT is an indicator of poor quality.

Accurate determination of the pathologic stage is critical to providing appropriate treatment for patients with bladder cancer. Therefore, many institutions have adopted a program of reviewing biopsy slides performed at non-affiliated institutions in the hope of improving the staging accuracy. With recent emphasis on proper pathologic analysis of TURBT specimens, **Borza et al. (#1024)** determined the impact on the management of 142 patients diagnosed with bladder cancer by re-reviewing the TURBT specimen from an outside institution. Agreement between the outside and in-house grade occurred in 96% of patients. Low grade tumors comprised 4% of total cases and downgrading accounted for all discrepancies. Agreement between the outside biopsy and cystectomy grade and the in-house and cystectomy grade occurred in 78% and 80% of cases, respectively. Downgrading accounted for 17% of the discrepancies in the outside biopsy comparison and 18% in the in-house comparison. The majority of discrepancies were cases where there was no remaining tumor at the time of cystectomy. Exact agreement in stage was noted in 95% of cases when comparing outside to in-house biopsy reports. Understaging accounted for 2% of the discrepancies. Comparison of outside report to cystectomy and in-house report to cystectomy revealed agreement in 21% and 20%, respectively. One of the discrepancies between the outside pathology and in-house report changed management. This patient had T1 disease on the outside pathology report, but T2 disease on the in-house review. The authors conclude that agreement in grade and stage between outside pathology reports and in-house pathology review occurred in the vast majority of cases. There was poor correlation between both the outside or in-house pathology review and the final pathologic stage at the time of cystectomy. Management was not impacted by re-review of outside TURBT specimens. These findings are in contradiction to many large studies. Moreover, the reclassification as divergent histology was reported.

Kirkali et al. (#1474) reported the results of EORTC Trial 30993, sequential chemo-immunotherapy with mitomycin-c and BCG in a randomized phase II study. 96 patients with carcinoma in situ were randomized to the study from 2001 to 2005. Patients received weekly MMC for 6 weeks followed by 6 weeks of BCG plus 3 further instillations after 3 weeks. All responders received 3 weeks of maintenance BCG every 6 months up to 3 years. The complete response rate was 70.8 % in the sequential therapy group and 66.7% in the BCG alone group. After a median follow up of 4.7 years, 47.9% in the MMC+BCG and 54.2% of the BCG alone patients had failed treatment. Sequential treatment was deemed feasible, but there was no indication of a synergistic effect. No further studies are planned at this time.

Chamie et al. (#1475), reporting for the Urologic Diseases in America Project, used linked SEER-medicare data to identify 513 patients with an incident diagnosis of high-grade non-muscle invasive bladder cancer from 1992-2002. Univariate and multivariable analyses were performed to measure associations between the independent variables such as age, gender, and medical comorbidities with surveillance, staging and

treatment strategies. Compliance was strongest for upper tract imaging and lowest for post operative MMC instillation. Approximately 15% of patients underwent the recommended cystoscopies and 22% urine cytologies. 39% of patients received at least one dose of BCG with only 12% receiving all 6 instillations. Sociodemographic factors were associated with variation in adherence to surveillance. The authors conclude that evidence from best practice guidelines was not regularly administered to this cohort of patients, with the greatest deficiency occurring in the administration of intravesical therapy. It is likely that the adherence to guidelines is higher in more recent years.

ADVANCED DISEASE

Another big focus at the AUA meeting was the relevance of peri-operative chemotherapy for invasive bladder cancer at the time of cystectomy. **Messing et al. (#1708)** performed a secondary analysis of the SWOG 8710 trial and showed that mixed histology urothelial cancers (UC) are at least as responsive to MVAC chemotherapy as pure UCs are, and that the presence of squamous or glandular differentiation in locally advanced bladder UC is a strong indication for the use of neo-adjuvant chemotherapy prior to cystectomy. Patients were stratified into pure urothelial carcinoma (n=236) and mixed histology (n=59) cohorts. All cause mortality was evaluated between the two groups using Cox regression models. The overall survival was better in the mixed histology patients (HR: 0.46; p=0.02). Additionally, down-staging to pT0 was almost twice that in the mixed histology group compared to that of the pure urothelial cohort.

Antebie et al. (# 1710) evaluated the completion rates of neoadjuvant (NAC) compared to adjuvant chemotherapy (AC) in the setting of radical cystectomy (RC) for muscle-invasive bladder cancer. They performed a retrospective analysis of patients who underwent RC by as single surgical team between 1992 and 2008. Patients who received NAC and those with high-risk bladder cancer receiving AC were identified and relevant data analyzed. Among the 95 patients who were offered NAC, 83 (87.5%) initiated NAC. 202 patients were eligible for AC based on pathology and 68 (33.5%) initiated AC (p<0.001). In the NAC group 55 received at least 3 cycles of chemotherapy, 21 completed 2 cycles as planned and 7 (8.5%) did not complete planned chemotherapy. In the AC group 48 completed at least 4 cycles. 20 (29.5%) could not complete the planned cycles (p=0.003). In agreement with previous studies, the authors found that when chemotherapy is indicated in patients with high risk bladder cancer, those offered NAC are more likely to initiate and complete the planned number of cycles compared to those offered adjuvant chemotherapy.

Survival statistics suggest a modest improvement in the survival of patients with muscle-invasive bladder cancer over the previous 25 years. **Nieder et al. (#1026)** evaluated if there have been any significant trends in cause of death over this time period in a patient population that includes a high percentage of Hispanics. The authors evaluated their single institution's tumor registry retrospectively for all cases of bladder cancer since the registry's inception in 1980. All cases were evaluated and analyzed by stage, age, sex and ethnicity at diagnosis. Between 1980 and 2004, they identified 1,436 cases of bladder cancer. 74% of patients were male and 26% were female. White, Black and Hispanics comprised 81%, 2%, and 14%, respectively. In the most recent decade, Hispanics comprised 23% of the cohort. Most patients were diagnosed with non-invasive vs. muscle-invasive disease: 81% and 19%, respectively. Non-contemporary patients had worse survival. 5-year overall survival in patients diagnosed in the 1980s, 1990s, and 2000s were: 46%, 54% and 55%, respectively. 10-year overall survival for those diagnosed in the 1980s and 1990s were 23.9% and 29.5%, respectively. Of the 1,055 of patients who died during the study period (73%), the cause

of death was bladder cancer, cardiopulmonary disease, and secondary malignancy in 22%, 36% and 8%, respectively. Of their cohort, over 50% were identified as tobacco users (including 21% who were current smokers at the time of their diagnosis). The authors conclude that a far greater percentage of patients expired from cardiopulmonary disease or a secondary malignancy, as opposed to bladder cancer. Tobacco usage likely plays a large etiologic role in the development of bladder cancer and other malignancies, as well as cardiopulmonary disease. This information must be considered when counseling patients with bladder cancer.

Wosnitzer et al. (#1706) report their outcomes for patients undergoing perioperative chemotherapy with either cisplatin-based or carboplatin-based chemotherapy preoperatively. 127 and 24 patients underwent cisplatin and carboplatin based regimens, respectively. There was a significant difference in stage (T2 45% vs. 31%; T3 8% vs. 32%, T4 17% vs. 6%; p=0.022) and age (mean 71.7 vs. 64 years; p=0.001) between the two groups analyzed. For both adjuvant and neoadjuvant chemotherapy, overall survival was significantly decreased in the carboplatin group (HR 0.31, CI 0.003-0.140, p=0.003). For both adjuvant and neoadjuvant chemotherapy, disease specific survival was significantly decreased in the carboplatin group (HR 0.229, CI 0.085-0.618, p=0.004). The authors concluded that the use of perioperative carboplatin chemotherapy is associated with reduced overall and disease specific survival compared to either methotrexate, vinblastine, doxorubicin/ adriamycin, and cisplatin (MVAC) or gemcitabine and cisplatin (GC) regimens. Several phase III trials have demonstrated that carboplatin is inferior to cisplatin for bladder cancer. However, the conclusions from this study may be due partly to patient selection.

Lee et al. (#1703) evaluated the perioperative complications in radical cystectomy patients treated with and without neoadjuvant chemotherapy. A 2:1 treatment:control study design was used to compare patients with cT2-4 bladder cancer treated with radical cystectomy over a 17-year period. Overall the cohort consisted of 124 cases and 197 controls. There was no difference in age, gender, ASA score, BMI, tobacco use, performance status, operative time, blood loss, urinary diversion type or length of stay between the two groups. The neoadjuvant chemotherapy group had a higher rate of postoperative blood transfusion (p=0.049). Complications were noted in 36% of patients who received neoadjuvant chemotherapy compared to 43% of those who did not (p=0.29). Patients > 75 years of age who received adjuvant chemotherapy were at an increased risk for complications compared to those who did not receive adjuvant chemotherapy (OR 3.0; 95% CI: 1.2-7.5). Neoadjuvant chemotherapy did not increase the perioperative complication rates for middle-aged patients undergoing cystectomy in this study. However, there was an increased risk of complications in the older patients receiving neoadjuvant chemotherapy. Accurate collection of this type of information can help guide the clinical decision making regarding integrated perioperative chemotherapy in bladder cancer.

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Debates on Bladder Cancer

Conference report

Highlights Bladder Cancer AUA 2010

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Conflicts of interest

The authors declare that there are no conflicts of interest.