Moderated Poster Session IV: Bladder Cancer Thursday, October 8, 4:00 – 5:00 p.m.

P50

A Comparative Survival Analysis of Nonbilharzial Squamous Cell Carcinoma vs. Transitional Cell Carcinoma After Radical Cystectomy

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Introduction and Objective: In Western countries, after transitional cell carcinoma (TCC), nonbilharzial squamous cell carcinoma (NBSCC) represents the second most common bladder cancer histological subtype. We decided to examine population-based rates of cause-specific survival (CSS) in patients with NBSCC of the UB treated with radical cystectomy (RC) and compared those to CSS of patients with TCC of the UB treated with RC. We tested the hypothesis that NBSCC confers worse survival than TCC.

Materials and Methods: We identified 5845 RC cases within a multiregional database. Of those, 243(4.2%) had pathologically proven NBSCC and 5602 (95.8%) had TCC histology. Cox regression analyses and competing-risks regression models addressed the effect of histological subtype at RC on CSS. Covariates consisted of age, gender, race, pathological stage and grade as well as of the year of surgery.

Results: The median follow-up of censored NBSCC cases was 43 months vs. 51 months for TCC patients. At RC, only 6.2% of NBSCC patients had organ confined disease vs. 16.4% of TCC patients ($p<0.001$). At 2 years, cancer-specific mortality of NBSCC patients with organ confined disease was 7.7% vs. 9.7% for TCC patients with organ confined disease at RC ($p=0.5$). At 2 years, the cancer-specific mortality of NBSCC patients with non-organ confined disease was 38% vs. 26.5% for TCC patients at 2 years ($p=0.01$) In multivariable analyses, performed on the entire population, presence of NBSCC increased the risk of cancer-specific mortality in a 1.4-fold fashion relative to TCC ($p=0.007$).

Conclusion: NBSCC is more frequently non-organ confined and has a worse prognosis than TCC. In consequence, efforts should be made to diagnose NBSCC at an earlier stage, with the hope of achieving better survival outcomes.

P51

mTOR Inhibitor RAD001 (everolimus) Has Significant Antitumor Activity in Bladder Cancer

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Introduction and Objective: mTOR (mammalian target of rapamycin) is an effector of nutrients and growth signaling pathways which plays a central role in the regulation of cell protein synthesis. Promising preclinical data for diverse types of tumors have led to rapid translation of mTOR inhibitors as anticancer therapy into the clinical setting. We examined whether mTOR inhibition by RAD001 (Everolimus) could be therapeutically efficacious in the treatment of bladder cancer.

Materials and Methods: The response of nine human urothelial carcinoma cell lines to mTOR inhibition was evaluated by cell viability assay, western blot, and cell cycle analyses. *In vitro* effects on angiogenesis were tested by using vascular endothelial growth factor (VEGF) ELISA kit. *In vivo*, the effect of RAD001 was determined on xenograft tumor model, in nude mice subcutaneously inoculated with two human bladder cancer cell lines, KU-7 and UM-UM13. Tumor cell proliferation and apoptotic index were determined by PCNA and TUNEL assays respectively. Tumor microvessel density was investigated by CD31 staining.

Results: RAD001 markedly inhibited proliferation of all bladder cancer cell lines in a dose-dependent manner sensitivity. FACS analysis showed that treatment with RAD001 for 48h, induced a cell cycle arrest in the G0/G1 phase in all cell lines, without eliciting apoptosis. RAD001 significantly inhibited the phosphorylation of S6 downstream of mTOR and VEGF production in all cell lines. Tumors weight from mice treated with RAD001 were significantly reduced as compared to placebo-treated mice. This growth inhibition was associated with significant decrease in tumors withouth changes in cell death.

Conclusion: Inhibiting mTOR signaling in bladder cancer models demonstrated remarkable antitumor activity both *in vitro* and *in vivo*. This is the first study showing RAD001 could be exploited as a potential therapeutic strategy in bladder cancer.

P52

A Comparative Survival Analysis of Adenocarcinoma vs. Transitional Cell Carcinoma After Radical Cystectomy

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Introduction and Objective: Adenocarcinoma of the bladder (ADK) is a rare histological subtype accounting for 0.5 to 2% of all bladder cancers. We decided to compare the cancer-specific mortality (CSM) rates in patients with ADK or transitional cell carcinoma (TCC) of the urinary bladder treated with radical cystectomy (RC).

Materials and Methods: We identified 7264 RC cases within nine Surveillance, Epidemiology and End Results registries. Of those, 183 (2.5%) had pathologically proven ADK and 7081 (97.5%) had TCC. Kaplan Meier depicted CSM rates after surgery in the study population. Cox regression analyses addressed the effect of the histological subtypes on CSM rates. Covariates consisted of pathological stage and grade, age, gender, race and year of surgery quartiles.

Results: The median follow-up of censored ADK cases was 61 months vs. 57 months for TCC patients ($p=0.3$). At RC, there was no statistically significant difference in the rate of organ-confined (OC) disease between ADK and TCC patients (13.7 vs. 16.0%; $p=0.3$). At 2 years after surgery, the CSM rate of ADK patients with OC disease was 18.2% compared to 19.8% for TCC patients ($p=0.5$). Similarly, non-organ confined (NOC) ADK and NOC TCC showed a virtually equal CSM at 2 years from RC (26.6% vs. 28.2% $p=0.7$) In multivariable Cox regression analyses performed on the entire population, histological subtype failed to reach the independent predictor status ($p=0.1$).

Conclusion: Our study demonstrate that ADK do not differ in stage at presentation when compared to TCC. Moreover, ADK of the urinary bladder is not associated with a worse prognosis than TCC histological subtype.

P53
Combined Modality Treatment with Bladder Preservation for Muscle Invasive Bladder Cancer
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Introduction and Objective: To evaluate the 5-year results of maximum transurethral resection with adjuvant chemo-radiotherapy (CRT) for treatment of muscle invasive bladder cancer.
Materials and Methods: 104 patients with muscle invasive transitional cell carcinoma (TCC) of the bladder who were amenable to complete transurethral resection. All patients received 3 cycles of chemotherapy (CXT) (gemcitabine & cisplatin) after the maximal resection of their tumours. This was followed by 20 sessions (180 - 200 cGy, each) of conventional radiotherapy (RXT) in the next 4 weeks. Two weeks later, all cases were re-evaluated by CT and cystoscopy. If no evidence of the bladder tumours (complete response (CR) a completion of the RXT with concurrent cisplatin to get a total dose of 6000 - 6500 cGy. On the other hand, if a recurrent invasive tumour was detected in this initial re-assessment, the patient did not receive any more RCT and was assigned to have salvage cystectomy.
Results: Complete response was achieved in 78.8% of cases after the initial CRT and tumour grade was found to be the most significant risk factor to predict this response (p=0.004). With a median follow up of 71 months (range 23 - 93 months) for patients with initial CR, 16.2% of cases showed muscle invasive recurrences and multifocality was the only significant risk factor for their development (p=0.003). Superficial recurrences were detected in 8.1% of cases with initial CR and were successfully treated with transurethral resection and intravesical bacillus Calmette-Guerin (BCG). Wereported distant metastasis in 24.3% of patients with initial CR and tumour grade, stage and multifocality were the most significant risk factors for this complication (p=0.002, 0.031, 0.006). No cases of contracted bladder or late gastrointestinal complications were demonstrated in this series. We have also shown that the presence of old bilharzial infestation in the bladder in association with TCC has no significant impact on the results of this trimodal therapy. Lastly, the 5-year overall survival rate for patients with initial CR was 67.6% and for the whole patients in this study it was 59.8%.
Conclusion: Maximum transurethral resection of the bladder tumour (TURBT) with adjuvant RCT can be considered as a treatment option for a selected group of patients with invasive TCC.

P54
A Population-Based Assessment of Perioperative Mortality After Cystectomy for Bladder Cancer
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Introduction and Objective: Large variability exists in the rates of perioperative mortality after cystectomy. Contemporary estimates range from 0.7 to 5.6%. We tested several predictors of perioperative mortality and attempted to devise a model for individual perioperative mortality prediction.
Materials and Methods: We relied on life tables to quantify 30, 60, and 90-day mortality rates according to age, gender, stage (localized vs. regional), grade, type of surgery (partial vs. radical cystectomy), year of cystectomy, and histologic bladder cancer subtype. We fitted univariable and multivariable logistic regression models using 5510 patients diagnosed with cancer of the urinary bladder and treated with either partial or radical cystectomy within 4 series of records between 1984 and 2004. We than externally validated the model on 5471 similar patients from 5 other series of records.
Results: At 30, 60, and 90 days, the perioperative mortality rates were respectively 1.1, 2.4, and 3.9%. Age, stage, and histologic subtype represented statistically significant and independent predictors of 90-day mortality. The combined use of these 3 variables and of tumor grade resulted in the most accurate model (70.1%) for prediction of individual probability of 90-day mortality after cystectomy.
Conclusion: The accuracy of our model could potentially be improved with the consideration of additional parameters, such as surgical and hospital volume or comorbidity. While better models are being developed and tested, we suggest the use of the current model in individual decision making and in informed consent considerations, as it provides accurate predictions in 7 out of 10 patients.

P55
Stage Distribution at Radical Cystectomy During the Last Two Decades
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Introduction and Objective: Improvements in diagnostic tools during the last two decades may have resulted in a more favorable stage distribution of bladder cancer at radical cystectomy (RC). We examined the pathological stage distribution at RC over the last two decades in a large population-based cohort and assessed the effect of the year of treatment on cancer-specific survival after RC for transitional cell carcinoma (TCC) of the urinary bladder.
Materials and Methods: We identified 5602 TCC cases treated with RC in nine SEER registries. Survival plots and Cox regression models addressed the effect of year of treatment at RC on stage at RC. Covariates consisted of age, gender, race, pathological stage and grade.
Results: Distribution of non-organ confined disease at RC was 79.2% for patients treated between 1988 and 1992 (n=1355, 24.2%), 82.8% in 1993-1997 (n=1535, 27.4%), 85.8% in 1998-2001 (n=1545, 27.6%) and 86.8% in 2002-2004 (n=1167, 20.8) [χ^2 trend test p<0.001]. The 2 year cancer-specific survival rates according to the year of treatment categories were as follows: 79.3% vs. 76.1% vs. 76.7% vs. 71.5% (p<0.001). In multivariable analyses, the risk of cancer-specific mortality was 1.02-fold higher in patients treated between 1993-1997 compared to those treated in 1988-1992, 1.006-fold higher in 1997-2001 and 1.3-fold higher in 2002-2004 (p=0.03).
Conclusion: At radical cystectomy, a more advanced pathological stage was recorded in recent years compared to two decades ago. Our results show that efforts should be made to diagnose TCC at an earlier stage, with the hope of achieving better survival outcomes.

P56
The Incidence of Prostate Cancer and Urothelial Cancer in the Prostate in Cystoprostatectomy Specimens
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Introduction and Objective: The current gold standard for muscle invasive bladder cancer is radical cystectomy with removal of the prostate and seminal vesicles. Potential functional consequences of this radical procedure include compromised potency and continence. A growing interest in prostate/sexuality sparing cystectomy in orthotopic neobladder candidates with either partial or total sparing of the prostate and neurovascular bundles has emerged, although recent evidence suggest only a marginal functional benefit. Our objective is to determine the incidence of occult prostate cancer and urothelial cancer of the prostate in cystoprostatectomy specimens conducted for muscle invasive bladder cancer.
Materials and Methods: A retrospective review of 83 male patients who underwent radical cystoprostatectomy for muscle invasive bladder cancer between April 2004 and March 2007 was conducted. The median age of our study group was 71 years. Pathologic findings of prostate/urothelial cancer in the prostate were identified. Clinically significant prostate cancer was defined as Gleason score > 6, tumor volume >0.5cc, extracapsular extension or perineural invasion.
Results: Our review yielded a 30% (± 10%, 0.95 CI) rate of prostate cancer, with 19% (± 8.5%, 0.95 CI) of total specimens being positive

for clinically significant prostate cancer. Urothelial cancer in the prostate was identified in 16% (± 8.5%, 0.95 CI) of patients, with an overlap with prostate cancer in 2 patients. The overall rate of an underlying cancer within the prostate of our cystoprostatectomy specimens was ~46% (± 10.7%, 0.95 CI).
Conclusion: These findings suggest that the oncological risk of leaving behind residual cancer may not justify the practice of prostate sparing cystectomies.

P57

Management and Outcome of Patients who had Unresectable Disease upon Exploratory Laparotomy for Bladder Cancer

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Introduction and Objective: Aborted cystectomy due to unresectable disease is not uncommon in patients with bladder cancer. Our aim was to review the outcome of these patients and evaluate various prognostic variables.
Materials and Methods: From 1993 to 2007, a total of 31 bladder cancer patients underwent an aborted radical cystectomy due to unresectable disease and form the basis of this report. Survival data were estimated by method of Kaplan and Meier, with Cox proportional hazards regression model used to evaluate associations between survival and variables studied.
Results: Mean age of patients was 66 years with median follow-up of patients alive 10 months. The 2-and 5-year overall survival (OS) were 41% and 0%, respectively. Twenty had a pelvic lymph node dissection (PLND) and 11 patients did not. Twenty-three patients received postoperative therapy, of which 8 received chemotherapy with the intent of surgical consolidation (only 2 were rendered resectable thereafter) and 15 received combined chemoradiation. OS was not significantly associated with hydronephrosis, concomitant CIS, performance status, history of superficial tumors, postoperative therapy and salvage cystectomy. Patients with pN2-3 had similar overall survival compared to those with pT4b (13 vs. 17 months, p=0.59). However, patients who underwent PLND were associated with prolonged OS compared to those who did not (24 vs. 10 months, p=0.09).
Conclusion: Outcome of patients with unresectable disease is dismal. Patients who had an aborted cystectomy due to unresectable disease may benefit from PLND prior to chemoradiation. Further refinements of clinical staging to better identify these patients preoperatively and offer them upfront chemotherapy are needed.

P58

Impact of Sub-Stage and Pathology Review on the Clinical Outcome of pT1 Bladder Cancer

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Introduction and Objective: Management of pT1 bladder cancer is controversial. We evaluated the impact of sub-stage and pathology review on the clinical outcome of a large series of primary pT1 bladder cancer patients treated with BCG.
Materials and Methods: The slides of 163 primary (first diagnosis) pT1 bladder tumors from two university hospitals (Rotterdam, the Netherlands n=69 and Toronto, Canada n=94) were reviewed and sub-staged, i.e. pT1micro-invasive (pT1m) and pT1extensive-invasive (pT1e), as previously described.[1] In some cases pT1 tumors were restaged to either pTa or pT2 as indicated by the reviewer. All 163 patients were initially managed conservatively (BCG). Grade review was done according the 1973 and 2004 classifications systems in two separate sessions. Multivariate analyses for progression and disease specific survival were performed with sub-stage, size, hospital, multiplicity, CIS, gender, age, grade-1973 and grade-2004 as variables.
Results: Mean follow-up was 6.44 years (range 0.3-21.3 yrs), 29 patients were female. Mean age was 69 years at first diagnosis. CIS was found in 55 (34%) cases. Fifty-two patients remained recurrence-free (32%). Cystectomy was performed in 34 (21%) patients, muscle invasion was found in 27 of these patients. Progression to pT2 or metastasis was observed in 47 (29%) patients and 26 patients (16%) died of their disease. The slides were reviewed and sub-staged as follows: 24 were reassigned to pTa, 40 pT1m, 93 pT1e and 6 pT2. Grade review resulted in 74 G2 and 89 G3 lesions according to the 1973 system and 37 low-grade and 126 high-grade lesions according to the 2004 system. In multivariate analyses, Sub-stage (P<.0001), CIS (p=.008) and female gender (p=.014) proved of independent significance for progression and sub-stage (p<.0001) and CIS (p=.016) for disease-specific survival.
Conclusion: Review pathology is indicated in pT1 bladder cancer. Sub-stage (pT1m and pT1e) was possible in all the cases and very predictive of pT1 bladder cancer behaviour. The risk of progression of micro-invasive and extensive-invasive pT1 bladder tumors is very different. Future studies may lead to the incorporation of sub-stage in the TNM classification system for urinary bladder cancer.

P59

Long-Term Follow-Up for Primary T1 High-Grade Bladder Cancer—Does BCG Really Prevent Progression?

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Introduction and Objective: Intravesical immunotherapy with bacillus Calmette-Guérin (BCG) is an established conservative treatment for high-grade (HG) T1 urothelial bladder cancer. Meta-analyses have demonstrated BCG's potential to prevent tumor progression. However, in these studies, the follow-up was short (median of 2.5 years) and they often included Ta tumors which carry a low risk of progression. Data about the long-term ability of BCG to prevent tumor progression to muscle-invasive disease are limited and most series included small number of patients. To answer these questions, we have analyzed the clinical outcome of primary T1-HG bladder cancer patients treated with BCG from two University hospitals.
Materials and Methods: From 1984 to 2006, 136 patients (Rotterdam n=49; Toronto n=87) were diagnosed with primary T1-HG tumors and treated conservatively at first intent. All patients (mean age: 67.7 years; 25 female patients or 18.4%) were treated with BCG induction (6 instillations). BCG failures were treated either by additional BCG, bladder preservation approaches or cystectomy. Progression and disease specific survival (DSS) were assessed. One uro-pathologist reviewed all primary T1-HG tumors slides and confirmed the diagnosis.
Results: Mean follow-up was 6.5 years (range 0.4-21.6 y). Kaplan-Meier analyses showed no significant differences for progression (p=.35) and DSS (p=.69) between the two hospitals. Fourty-seven patients (35%) never recurred while 47 (35%) had non-muscle invasive recurrence. Fourty-two patients (30%) progressed to muscle invasive disease, 25 of them underwent a cystectomy whereas 9 had a bladder preservation approach. Median time to progression was 2.1 years. Sixteen of these 42 patients (38%) progressed after 3 or more years of follow-up and 22 (16%) patients died of bladder cancer. Ninety-six patients (71%) had no evidence of disease at last follow-up. Age, tumor size and multiplicity were not predictive for progression while presence of CIS (p=.13) and female gender (p=.10) showed a trend towards but did not reach statistical significance.
Conclusion: This report on a series of primary T1-HG bladder tumors with long-term follow-up supports conservative treatment with BCG as a reasonable approach for these patients. Nevertheless, T1-HG is an aggressive disease entity as 30% of the patients progressed and 16% died of their disease. More than 1/3 of cases which progressed occurred 3 years after initial BCG thereby questioning the long-term ability of BCG to prevent bladder tumor progression. Markers are clearly need-

ed to help differentiating between HG T1 tumors at high or low risk of progression.

P60

What is the Long-Term Prognostic Value of Pro-Apoptotic, Anti-Apoptotic, Proliferation and Invasiveness Molecular Markers in Patients Treated with BCG for High-Risk Non-Muscle Invasive Bladder Cancer?

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Introduction and Objective: To evaluate the long-term prognostic value of pro-apoptotic, anti-apoptotic, proliferation and invasiveness molecular markers in predicting the outcome of high-risk non-muscle invasive bladder cancer treated with intravesical BCG therapy. Most previous series have analyzed the short-term prognostic value of these markers only

Materials and Methods: A prospective study included 42 patients presenting with high-risk non-muscle invasive bladder cancer (high grade or T1 tumors or multiple rapidly recurrent tumors refractory to intravesical chemotherapy) treated with transurethral resection and intravesical BCG. Transurethral tumour resection samples were analysed for the molecular markers p53, p21 waf1/cip, Bcl-2, Cyclin D1 and metallothionein 9 (MMP9) using immunohistochemical techniques. Frequency of positivity measured as a percentage was then assessed for interaction with clinical tumor characteristics (stage, grade, multifocality, size) and the tumor outcome variables of recurrence and progression using univariate and multivariate analyses as well as Kaplan-Meyer curves (SSPS statistical package).

Results: There were 38 men and 4 women (mean age 68.3 years) and median follow-up was 88 months (mean 99, range 14-212 months). In this high-risk population, the overall recurrence rate was 61.9% and progression rate was 21.4%. As expected, in multivariate analysis, grade was predictive of recurrence and stage predictive of progression ($p<0.05$). In multivariate analysis adjusting for tumor stage, grade, multifocality and size, the only predictor of recurrence-free survival was p21 (p 0.041), while progression-free survival was predicted by Cyclin D1 (p 0.024) and MMP9 (p 0.054). Interestingly, the statistically significant predictive value of these markers at 5 years was maintained at longer follow-up both for recurrence and progression, MMP 9 only becoming of borderline significance (p 0.054).

Conclusion: Long-term response to BCG therapy of high-risk non-muscle invasive bladder cancer may be predicted by molecular markers. These represent different elements of the carcinogenic pathway and may offer improved prediction compared to grade and stage alone. Larger series are needed to confirm these findings including new pathways like the FGFR-3.

P61

Does Screening for Bladder Cancer Produce a Stage Migration Towards Non-Muscle Invasive Cancers?

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Introduction and Objective: Over 25% of new bladder cancer cases are still muscle-invasive at first diagnosis. It is actually unproven whether screening could lead to a stage migration. We evaluated the potential benefits of bladder cancer screening in a very high-risk patient population. Aristolochic acid nephropathy (AAN), a progressive renal interstitial fibrosis frequently associated with urothelial malignancies was initially reported in a Belgian cohort of patients after the intake of slimming pills containing a Chinese herb. Upper-tract and bladder urothelial carcinoma are dramatic complications after aristolochic acid nephropathy.

Materials and Methods: We followed 47 patients (46 women, 1 man) affected by ANN nephropathy. We established the cumulative incidence of bladder cancer during prospective screening cystoscopies every 6 months during a 10-year follow-up starting 5 years after exposure. We analyzed whether this screening protocol influenced bladder tumors stage at presentation.

Results: Bladder cancer was diagnosed in 20/47 patients (42.5%), 68 to 169 months after cessation of AA exposure. At first diagnosis, among the 45 patients who followed all their scheduled cystoscopies, 15 carcinoma in situ, 2 low-grade Ta urothelial carcinoma and 1 high-grade T1 cancers were diagnosed but no muscle-invasive tumor. Among these 20 patients with non invasive tumors treated conservatively, during follow-up 2 developed progressive disease requiring cystectomy and are alive, whereas 4 had non muscle-invasive tumors treated conservatively. None of these patients died of bladder cancer. In contrast 2 women who declined follow-up for 2 years were diagnosed with advanced disease at the time they presented with symptoms and died of metastatic disease.

Conclusion: In this very high risk and unique patient population, screening for bladder cancer using cystoscopies every six month resulted in a shift in bladder cancer presentation with all tumors presenting at a non muscle invasive stage except 2 patients who declined follow-up and were diagnosed with invasive cancer at the time of their symptoms. Bladder cancer screening even in a very high-risk population may result in a dramatic change in the presentation of cancers at an earlier stage. The optimal screening schedule and high-risk populations remain to be defined.

P62

Cost Analysis of a Single Instillation of Mitomycin C After Transurethral Resection of Bladder Tumor in the Québec Health Care System

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Introduction and Objective: The current recommended management strategy for recurrent superficial urothelial carcinoma of the bladder involves a single post-operative intravesical dose of Mitomycin C. Only a minority of patients receive it, however, in part due to its potential associated costs. We set out to perform a 5-year cost-analysis of this strategy within the Québec health care environment.

Materials and Methods: A decision-analytic model was utilized to evaluate the health-economic consequences of "one-shot" Mitomycin C therapy after transurethral bladder tumor resection (TURBT). Input estimates for 5- year recurrence rates (50%) and Mitomycin C efficacy (absolute risk reduction of 15%) were identified via a systematic literature search and data from meta-analyses. The 2008 treatment costs were determined from current Québec Health Care policies, including physician fees, Mitomycin C drug costs, TURBT and cystoscopy, as well as institutional hospital admission. A sensitivity analysis was also performed. Societal costs such as work absences and productivity loss were not included in the analysis. The model was limited to a 5-year closed follow up period, and inherent assumptions included low associated morbidity and mortality, constant recurrence rates in both treatment strategies, and no cross-over was permitted between groups. The assumed indifferent progression rate between groups would not impact incremental costs and effectiveness of the strategies, and thus we excluded the progression costs from our model.

Results: Overall 5-year analysis reveals that the five-year cumulative cost of the TURBT plus Mitomycin C strategy is more cost effective, saving the Medicare system $189.00/ patient over 5 years ($8571.00 and $8382.00 for TURBT vs. TURBT+ Mitomycin C, respectively). Calculated differences take into account the avoidance of cystoscopic surveillance, urinary cytology and re-operative follow-up costs associated with multiple recurrences, as compared to less frequent occurrences in the Mitomycin C group. The sensitivity analysis revealed a dominance of Mitomycin utilization over TURBT alone.

Conclusion: Routine utilization of Mitomycin C after TURBT is not associated with increased costs to the health care system. In fact, there is a significant cost savings to the health care system over a 5-year follow-up

period. Additionally, non-quantified patient benefit and the secondary societal advantage of gained wages and productivity owing to a decrease in recurrence and surgery could further alter the cost-analysis model, resulting in an increasingly favourable cost benefit. The unequivocal sensitivity analyses further underscores the robustness of our findings.

P63

Surveillance Guidelines Based on Recurrence Patterns Following Radical Cystectomy for Bladder Cancer: The Canadian Bladder Cancer Network Experience

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Introduction and Objective: Bladder cancer often recurs after surgical intervention and there is debate with regards to the optimal follow-up strategies. We sought to review our data on the recurrence patterns following radical cystectomy with the aim to establish appropriate surveillance protocols for patients with localized and locally advanced bladder cancer.

Materials and Methods: We collected and pooled a database of 2,287 patients who have undergone radical cystectomy for carcinoma of the bladder between 1993 and 2008 in 8 different centers across Canada. Complete recurrence information was available in 1,606 patients. We looked at recurrence patterns with regards to sites and time to recurrence. The sites were divided into pelvic, retroperitoneal and distant.

Results: Total of 825 patients developed recurrence According to location, half were distant (218) with the remaining divided into: 113 pelvic (25.2%), 65 retroperitoneal (14.5%) and 53 to multiple sites (11.8%). Of those that were labelled as distant, most common sites were lungs (42%), bone (35.5%) and liver (27%). Median time to recurrence for entire population was 10.1 months (range 0 to 192.4) with 90% and 97% of all recurrences happening by 2 and 5 years post-cystectomy, respectively. When stratified according to stage, tumors with positive nodes (pTxN+) were more likely to recur than extravesical node-negative tumors (>pT3N0) and organ-confined node-negative tumors (≤pT2N0) (57% vs. 40.1% vs. 21.5% respectively). Similarly, pTxN+ tumors had a shorter median time to recurrence (9.1 months, range 0 to 71.6 months) compared to >pT3N0 tumors (9.5 months, range 0 to 69.5 months) and ≤pT2N0 tumors (13.7 months, range 0 to 192.4 months).

Conclusion: Differences in recurrence patterns between the different subgroups after radical cystectomy suggest the need for varying follow-up protocols for patients in each. Strict surveillance is recommended within the first two post-operative years with office visits, blood testing and chest X-rays every 3-6 months. Triphasic CT to assess upper tracts, abdomen, and pelvis are recommended every 6 months in the first 3 years then annually for organ confined node-negative tumors and every 3 months in the first 2 years then every 6 months for the next 2 years then annually thereafter for extravesical node-negative and node-positive tumors.

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Florescence Cystoscopy with Hexaminolevulinate (HAL) Improves Detection Rate of Ta and T1 Bladder Cancer and Reduces Recurrence Following TURBT at Nine months

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Introduction and Objective: To compare fluorescence guided (HAL) and white light (WL) cystoscopy for detection of Ta/T1 bladder cancer, and to compare the 9 month recurrence rates following WL + HAL or WL only resection of identified tumors.

Materials and Methods: Multicenter randomized, phase III study conducted in the US, Canada and Europe. Eligible patients at high risk for recurrence had initial or recurrent multiple papillary tumors, or patients with at least one tumor that recurred within 12 months were randomized to WL only or WL+HAL fluorescence cystoscopy. All patients had HAL instilled prior to cystoscopy, but those randomized to WL, never had fluorescence cystoscopy and just underwent TURBT, while those randomized to HAL were first inspected under WL and then underwent a second inspection and mapping under blue light. All suspicious areas were biopsied followed by TURBT in both groups. Completeness of resection was checked in blue light for patients randomized to HAL. Follow up at 3, 6 and 9 months was with WL. Patients with high grade and/or TIS cancers also received 6 weekly instillations of BCG after the index TURBT.

Results: 766 patients meeting entry criteria) were randomized and of the patients randomized to HAL, 278 were diagnosed as Ta/T1 with central pathology review (ITT). Within-patient comparison showed that in 16.9% of these patients at least one additional Ta/T1 tumor was detected with HAL compared to WL (p=0.0005). Also in the HAL arm, 41 patients had CIS, and 13 of them (32%) were diagnosed only with HAL, an improvement in CIS detection rate of 46%. False positive rates were 12% for HAL and 10% for white light. Comparing the 402 patients with Ta/T1 lesions (202 white light, 200 HAL) who completed the per protocol study, a significant reduction in tumor recurrence was seen in the HAL arm: 72 (36%) compared to 92 (46%) in the white light group (p =0.029).

Conclusion: Inpatients with Ta/T1 bladder cancer, HAL fluorescence cystoscopy improves detection and completeness of resection compared to WL leading to a reduction in recurrence rates at nine months.

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Survey on the Work-Up and Screening of Hematuria Among General Practitioners in Québec

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Introduction and Objective: Hematuria is one of the most common findings on urinalysis in patients encountered by general practitioners (GP). It can also be the first presentation of a serious urological problem in many instances. As such, we sought to shed the light on the current practices adopted at the primary care level in its work-up and screening.

Materials and Methods: We conducted a survey which was mailed in both French and English to over 8000 registered GPs in the province of Québec. The questions covered each physician's personal approach to men and post-menopausal women with painless gross hematuria or with asymptomatic microscopic hematuria as well as screening techniques, general knowledge with regards to urine collection and sampling, and referral patterns.

Results: Of the surveys mailed, 599 (7.5% response rate) were returned. Mean years from graduation was 24.8 years (median=25, range 3 to 58). In an older male with painless gross hematuria, only 64% of GP recommended further evaluation by a urologist with 8% opting to reassure the patient and see him in follow-up. On the other hand, in a post-menopaUSl woman with two consecutive events of significant microscopic hematuria, only 48.6% recommended referral to urology despite the fact that 95% of GPs stated that microscopic hematuria is associated with bladder cancer. Interestingly, 47% of GPs perform a routine screening urinalysis with the annual physical examination on all male and female patients and 26% do not order it in asymptomatic patients regardless of risk factors. Finally, when asked what represented significant microscopic hematuria on two consecutive urine samples, only 42.1% responded ≤3 red blood cells per high-power field whereas the majority of GPs (50%) stated >10/hpf.

Conclusion: There seems to be reluctance amongst primary care physicians to refer patients with gross or significant microscopic hematuria to a urologist for further investigation. A higher level of suspicion should

be encouraged in order to possibly detect serious conditions and offer earlier intervention when possible.

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Combining mTOR Inhibitor (RAD001) with Ionizing Radiation: A Novel Strategy for the Treatment of Bladder Cancer

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Introduction and Objective: Radiation therapy for invasive bladder cancer allows for organ preservation but systemic toxicity and local control remain problematic. As such, there is a need to increase radiosensitization of tumor cells to improve efficacy. The aim of this study was to investigate if mTOR (mammalian target of rapamycin), a downstream kinase of the PI3K/Akt growth pathway, may be a target for bladder cancer therapy.

Materials and Methods: A panel of nine representative human urothelial carcinoma cell lines reflecting different stages of bladder cancer was screened for their sensitivity to the mTOR inhibitor, RAD001. Clonogenic assays were performed in order to address the effects of ionizing radiation (IR) alone and with RAD001. The expression of Akt and mTOR as well as the mTOR substrate, S6, was assessed by Western blots, including in their phosphorylated state. Cell cycle analysis was performed using flow cytometry. In vivo, nude mice were injected with KU7 cells. Treatment with RAD001 (1.5 mg/kg, daily), fractionated IR (total 9 Gy), and in combination of RAD001 and IR was followed over 4 weeks. Tumors were harvested upon the completion of the treatment. Immunohistochemical staining was performed to assess the level of proliferation, angiogenesis and apoptosis in all the groups.

Results: RAD001 was a very potent growth inhibitor for the nine screened bladder cancer cell lines. A G0/G1 as well as a G2 arrest was seen in the combined treatment compared to either treatment alone in the cell lines tested. Western blots revealed expression of activated key signalling molecules of the mTOR pathway. Moreover RAD001 effectively inhibited the mTOR downstream signal. A significant decrease in cellular colony formation was observed in the combined treatment when compared to RAD001 or radiation alone ($p<0.05$). Furthermore, our in vivo data confirm our in vitro data, whereas a significant decrease in tumor weight was observed in the combined treatment (90% decrease, $p<0.001$) when compared to either treatments alone (60% decrease for RAD001 alone, $p<0.05$; 77% decrease for IR alone, $p<0.05$). The immunohistochemical staining indicated marked inhibition of cellular proliferation in the combined treatment compared to either treatments alone, as well as lower levels of angiogenesis. No change in apoptotic cell death was observed. These findings point to an additive and possibly a synergistic effect of the combined treatment of RAD001 and IR.

Conclusion: The inhibition of mTOR signalling appears promising as a therapeutic modality for bladder cancer, especially in the context of combination with radiation therapy.