

# Podium Session 3: Oncology (Bladder)

## June 24, 2013, 1050-1150

### POD-03.01

#### Utilization and Impact of Perioperative Chemotherapy for Muscle-invasive Bladder Cancer: Are We Achieving the Achievable?

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**Introduction and Objectives:** The utilization of perioperative chemotherapy for bladder cancer in the general population and the survival benefit associated with therapy is not well described. Here we report practice patterns and outcomes associated with perioperative chemotherapy in the general population of Ontario, Canada.

**Methods:** Electronic records of treatment were linked to the population-based Ontario Cancer Registry to identify all patients who underwent cystectomy for bladder cancer in Ontario 1994-2008. Utilization of neoadjuvant (NACT) and adjuvant (ACT) chemotherapy was compared across 3 study periods: 1994-98, 1999-03, 2004-08. Logistic regression was used to analyze factors associated with use of NACT/ACT. A Cox model and propensity score analysis was used to explore the association between ACT and survival.

**Results:** 2738 muscle-invasive cases were identified. While use of NACT did not change substantially over the 3 study periods (5%, 3%, 6%;  $p=0.004$ ), utilization of ACT increased with time (16%, 19%, 23%;  $p=0.001$ ). In adjusted analyses younger age and less comorbidity were associated with greater utilization of NACT and ACT as was higher T stage and lymphovascular invasion/node positive disease (OR 7.2, 95% CI 5.5-9.5). Five year overall (OS) and cancer-specific survival (CSS) for all muscle-invasive cases were 30% (95% CI 28-31%) and 34% (95% CI 32-36%) respectively. In Cox analysis T3/T4 tumours (HR 1.7, 95% CI 1.6-2.0), node positive disease (HR 1.9, 95% CI 1.7-2.1), and lymphovascular invasion (HR 1.8, 95% CI 1.6-2.1) were independently associated with inferior OS. Utilization of ACT was associated with improved OS (HR 0.70, 95% CI 0.6-0.8) and improved CSS (HR 0.70, 95% CI 0.6-0.8).

**Conclusions:** Despite accumulating evidence and guidelines, NACT/ACT remains substantially underutilized in routine clinical practice. Our results suggest that ACT is associated with a substantial survival benefit in the general population.

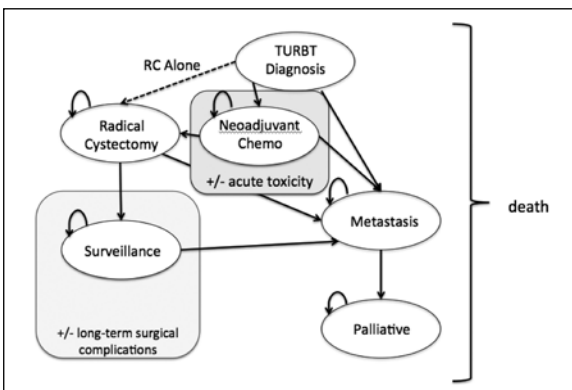


Fig. 1. POD-03.02.

### POD-03.02

#### Comparing Radical Cystectomy with and without Neoadjuvant Chemotherapy to Radiation Therapy-based Bladder Conservation Approaches for Muscle-invasive Bladder Cancer: A Decision Analysis

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**Introduction and Objectives:** The side effects and survival of three treatment strategies for muscle invasive bladder cancer (MIBC) differ substantially and controversy exists over which treatment maximizes survival and quality-of-life (QOL).

**Methods:** We evaluated three treatment strategies for high risk, MIBC using a Markov probabilistic, microsimulation model based on formal literature review using patient perspective and a lifetime time horizon (see Markov diagrams below). Patients of varying ages (mean 68, SD 7) with newly diagnosed MIBC of varying grade and lymph node positivity (T2-T4, N0/N+) were entered into the model. Three strategies were evaluated: (1) immediate radical cystectomy (RC); 2. immediate neoadjuvant chemotherapy followed by radical cystectomy (NC&RC); 3. trimodal therapy consisting of immediate pelvic and nodal radiation with concurrent systemic chemotherapy followed by cystectomy for patients without complete remission (TMT). Outcomes were life expectancy (LE) and quality-adjusted life expectancy (QALE).

**Results:** LE of 9.6 years was optimized with NC&RC treatment, while QALE of 6.9 years was maximized with TMT treatment. RC had the lowest LE

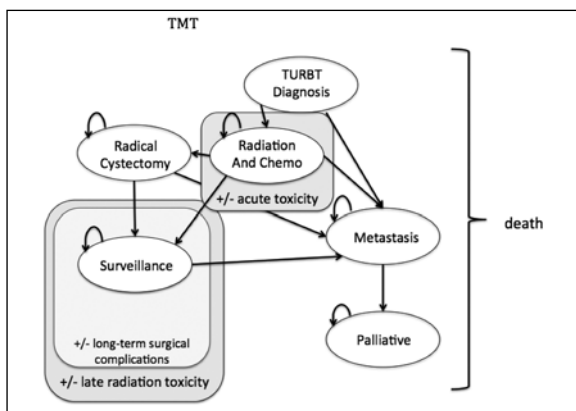


Fig. 2. POD-03.02.

(9 years) and QALE (6.4 years) compared to other treatments. Across all ranges of patient age, disease severity and gender, TMT was the decision that most often maximized QALE. In one-way sensitivity analysis, NC&RC only maximized QALE over TMT when the disutility of living without a bladder was less than 0.01 (Fig. 1, Fig. 2).

**Conclusions:** For patients with newly diagnosed MIBC, management with either neoadjuvant chemotherapy and radical cystectomy or radical radiation therapy with concurrent systemic chemotherapy with or without cystectomy offers improved life expectancy and quality-adjusted life expectancy compared to radical cystectomy alone.

### POD-03.03

#### Incidence, Characteristics, and Implications of Thromboembolic Events in Patients with Muscle Invasive Bladder Cancer Undergoing Cisplatin Based Neo-adjuvant Chemotherapy

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**Introduction:** Neo-adjuvant chemotherapy (nCT) is recommended to improve survival in patients with muscle invasive bladder cancer (MIBC). Cancer patients receiving chemotherapy are at risk for thrombo-embolic events (TEE). The impact of nCT on the development of TEE in MIBC patients has not been described before. We investigated the incidence and characteristics of TEE during nCT for MIBC.

**Methods:** A retrospective single tertiary centre study was carried out on 67 unselected consecutive patients who underwent cisplatin based nCT for MIBC from 2006 to 2012. The median time of follow-up from diagnosis was 14 months (range 4-73 months). We analyzed the incidence and timing of TEE (venous or arterial thrombosis, overt or incidentally detected pulmonary embolism on staging imaging). Stratification of TEE risk according to Khorana criteria (based on baseline haemoglobin, platelet and leukocyte count, BMI and tumour site), which was established for cancer patients treated with chemotherapy, was calculated for all patients. Log rank test was used to compare survival between patients who developed TEE and those who did not.

**Results:** The incidence of TEE in patients undergoing nCT was 15%. The Khorana criteria indicated high TEE risk in most patients with MIBC. TEE were usually detected after the 4th nCT cycle. Half of the TEE events were detected as asymptomatic pulmonary embolism in staging chest CT. 50% of the patients developing TEE progressed or died before their planned post-nCT radical cystectomy (RC) and in the others delay in RC was common. TEE was associated with worse outcome- Median survival of patients who developed TEE was 13 months as compared to 42 months in those who did not developed TEE ( $p=0.0136$ , HR 0.1816 (95% CI 0.04690-0.7036)).

**Conclusions:** In our series which is limited by a relatively small sample size and retrospective nature, TEE was very common in MIBC patients undergoing nCT and associated with poorer survival as well as cancellation or delay in post-nCT RC. These observations are novel and external and prospective validation is warranted.

### POD-03.04

#### The Impact of Surgeon-related Parameters on Outcomes for Muscle-invasive Bladder Cancer

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**Introduction and Objective:** Our objective was to assess the impact of various surgeon characteristics on outcomes for patients requiring radical cystectomy (RC) for muscle-invasive bladder cancer (MIBC).

**Methods:** A retrospective cohort undergoing RC for MIBC between Jan 1, 1993 and Dec 31, 2011 was assembled. Salvage & palliative RCs, and those ineligible for platinum-based perioperative chemotherapy (PC) were excluded. Variables of interest were RC volume, uro-oncology fel-

lowship, use of PC, nodal yield (NY), and positive surgical margin rates. Overall (OS) and cancer-specific survival (CSS) were the outcomes studied. Survival curves and cox-proportional hazard modeling (adjusting for age, gender, comorbidity (Charlson comorbidity index), year of RC, use of PC, margin status (MS), NY and cancer stage) were used.

**Results:** Of the final cohort of 205 patients (30 months median follow up), 34 (16.6%), 30 (14.6%), and 141 (68.8%), underwent RC by low volume (LV, <5 RC/year), intermediate volume (IV, 5-10 RC/year) and high volume (HV, >10 RC/year) surgeons, respectively. All IV and HV surgeons were uro-oncology fellowship trained, and more often used neo-adjuvant chemotherapy ( $p=0.054$ ) compared to LV surgeons. Median nodal yield increased (LV= 6.5, IV = 13, HV = 15.5,  $p<0.0001$ ) with surgeon volume. In unadjusted survival analyses, HV surgeons had better median CSS (HV: 129.9 months vs. LV+IV: 29.9 months,  $p=0.0012$ ) and OS (HV = 81.6 mo vs. LV+IV = 27.7 months,  $p=0.0085$ ). In adjusted Cox-models, HV surgeons had improved CSS (HR = 0.51, 95% CI = 0.30-0.86,  $p=0.011$ ) and OS (HR = 0.60, 95% CI 0.38-0.93,  $p=0.024$ ), while PC, MS and NY were not significantly associated with either (with or without surgeon in the model).

**Conclusions:** High volume uro-oncologists possess traits that improve outcomes by means beyond concrete aspects of care such as negative MS, using PC and performing adequate lymphadenectomy. Our results suggest that MIBC patients are best managed by high volume, uro-oncology fellowship-trained urologists in a multidisciplinary setting.

### POD-03.05

#### Predictors of Longer Preoperative Delays Prior to Radical Cystectomy (RC) in Patients with Bladder Cancer in Quebec

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**Introduction and Objectives:** Bladder cancer (BC) is the second most common urological cancer in Canada. We reported in 2006 that preoperative delays for BC surgery have been progressively increasing over time, with a detrimental effect of longer delays on mortality (1). The aim of this study is to identify predictors associated with longer preoperative delays.

**Methods:** We conducted a retrospective cohort study using data from patients who underwent RC for BC from 2000 to 2009 in Quebec. The cohort was obtained with the linkage of two administrative databases: the RAMQ database, and the ISQ database. Predictors of longer delays were analyzed using logistic regression.

**Results:** 2988 patients met inclusion criteria and were included in this study. Predictors associated with a delay longer than 30 days between 1st GP visit to 1st urologist visit were gender (OR: 2.43, 95% CI: 1.87-3.15 for women), living in Quebec City region (OR: 1.73, 95% CI: 1.26-2.37), and having had a GP visit in 2009 (OR: 2.05, 95% CI: 1.21-3.48). Predictors associated with a delay longer than 30 days between 1st urologist visit and 1st cystoscopy were gender (OR: 0.64, 95% CI: 0.51-0.81 for women), age (OR: 1.26, 95% CI: 1.03-1.55), having cystoscopy in a hospital facility near Quebec City (OR: 1.80, 95% CI: 1.31-2.47). Predictors associated with a delay longer than 12 weeks between 1st TURBT and RC were age (OR: 1.30, 95% CI: 1.03-1.62), region where surgery was performed (OR: 2.05, 95% CI: 1.47-2.87), and having RC performed by a surgeon with an annual case load higher than 10 (OR: 1.61, 95% CI: 1.16-2.23). Delays longer than 12 weeks between TURBT and RC resulted in 14% increase in mortality (HR: 1.14, 95% CI: 0.96-1.35).

**Conclusion:** Our analysis revealed that gender, age, year of RC and type of hospital facility, were associated with longer delays in Quebec. Women appeared to suffer significantly longer delays prior to RC.

**POD-03.06****Process of Care Variables Explaining the Influence of Surgical Volumes in Bladder Cancer Outcomes**

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**Introduction and Objectives:** Procedure volume is related to operative morbidity and mortality after cystectomy. However its effect on cancer-specific survival is not well characterized. Here we describe the relationships between hospital volume, surgeon volume, and late survival after cystectomy for muscle invasive bladder cancer (MIBC).

**Methods:** Electronic records of treatment and surgical pathology reports were linked to the population-based Ontario Cancer Registry to identify all patients who underwent cystectomy for MIBC in Ontario, Canada. Process of care factors examined to explain any volume effect included adjuvant chemotherapy use, lymph node dissection (LND) and surgical margin status. Volume was divided into quartiles and determined based on mean annual number of hospital/surgeon cystectomy cases per 5-year period. A Cox proportional hazards regression model was used to explore the associations between volume and survival.

**Results:** The study included 2738 cystectomy cases for MIBC treated between 1994 and 2008. Five-year overall (OS) and cancer-specific survival (CSS) for all cases were 30% (95% CI 28-31%) and 34% (95%

CI 32-36%). In comparing the highest volume quartile to the lowest, the higher volume hospitals were more likely to have utilized adjuvant chemotherapy (27% vs. 15%,  $p < 0.001$ ) and were more likely to have performed a LND (83% vs. 53%,  $p < 0.001$ ). The highest volume hospitals were also associated with a lower 90-day mortality (6% vs. 10%,  $p = 0.032$ ). Low volume hospitals were associated with lower 5 year OS 28% (95% CI 24-31%) and CSS 32% (28-36%) compared to high volume centres 35% (31-38%) and 38% (33-42%) respectively. In multivariate analysis, hospital volume was associated with both cancer specific ( $p = 0.013$ ) and overall survival ( $p = 0.002$ ). Compared to the highest volume centres the HR for OS in the low volume centres was 1.24 (95% CI 1.09-1.41); the HR for CSS was 1.21 (95% CI 1.04-1.40). When individual surgeon volume was added into the model, almost all of the hospital volume effect on OS and CSS disappeared (1.07 [95% CI 0.90-1.27] and 1.05 [95% CI 0.86-1.27] respectively). The point estimate for the volume effect diminished, but did not disappear when LND was included in the model whereas utilization of adjuvant chemotherapy and margin status did not mediate the effect.

**Conclusions:** Greater cystectomy volume is associated with improved 5 year CSS and OS in MIBC in the general population and this effect appears to be explained best by individual surgeon volumes as opposed to hospital volume. Other process of care variables measured in this study do not appear to mediate the volume effect other than quality of LND.