

# Delivering high-quality care to patients with muscle-invasive bladder cancer: Insights from routine practice in Ontario

Christopher M. Booth, MD, FRCPC;\* D. Robert Siemens, MD, FRCSC†

\*Division of Cancer Care and Epidemiology, Queen's University Cancer Research Institute, and Departments of Oncology and Public Health Sciences, Queen's University, Kingston, ON; †Division of Cancer Care and Epidemiology, Queen's University Cancer Research Institute, and Departments of Oncology and Urology, Queen's University, Kingston, ON

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**B**ladder cancer is the 6th most common cancer in Canada and the 8th leading cause of cancer death.<sup>1</sup> Current dogma would suggest that radical cystectomy, including an “adequate” pelvic lymph node dissection, preceded by neoadjuvant chemotherapy (NACT) is our closest approximation to a treatment standard for those with muscle invasive bladder cancer (MIBC). However, one could argue that this treatment paradigm is problematic given the limitations of available evidence and practical challenges in delivering “optimal” care in routine clinical practice.

The lack of contemporary randomized controlled trials (RCTs) systematically comparing radical cystectomy to bladder-sparing approaches has contributed to discordance in definitive local therapy recommendations in international treatment guidelines.<sup>2-6</sup> Ambiguity in the impact and boundaries of a lymph node dissection at cystectomy likely explain the limited uptake of extended dissections (as measured by lymph node yields) in routine practice,<sup>7</sup> including variations in practice in higher-volume, academic centres.<sup>8</sup> There is consistent evidence that provider (hospital and surgeon) cystectomy volume is strongly associated with patient outcomes;<sup>9-11</sup> this evidence has led to calls for centralization of care for other complex surgical procedures.

Given the high relapse rates after definitive local therapy,<sup>12-14</sup> practice guidelines generally endorse the use of cisplatin-based NACT for patients with MIBC on the basis of Level 1 evidence from RCTs and meta-analysis.<sup>3-5,15,16</sup> Despite this, uptake of NACT in the general population is much lower than expected for the potential pool of appropriate candidates, perhaps dramatically so for those patients in Canada.<sup>17</sup> The same guidelines either do not support adjuvant chemotherapy (ACT), or provide only weak support, due to a lack of information from adequately powered RCTs. Recently, however, results of 3 contemporary randomized trials,<sup>18-20</sup> an updated meta-analysis,<sup>21</sup> and 2 large observa-

tional studies<sup>22,23</sup> have all consistently demonstrated that ACT also provides benefit to patients.

We have recently published a series of reports describing the results of a large population-based study of practice and outcomes of bladder cancer in Ontario.<sup>23-27</sup> We used the Ontario Cancer Registry and linked electronic records of treatment to describe the care of all patients in Ontario with bladder cancer treated during 1994 and 2008. This cohort includes 3879 patients treated with cystectomy and 1380 patients treated with curative radiotherapy in routine clinical practice. In this commentary, we highlight some key findings from our studies to provide some insight and suggested future directions to improve the quality of care and subsequent outcomes of patients with bladder cancer in Canada.

## Local management of bladder cancer

During 1994 and 2008, 5259 patients with bladder cancer underwent definitive surgery or radiotherapy (RT) in Ontario.<sup>24</sup> Use of cystectomy increased over time while RT decreased: 22% of all patients were treated by RT during 2004 and 2008. We found substantial regional variation in the proportion of cases undergoing RT (range: 16%-51%) that was not explained by differences in case mix. Five-year cancer-specific survival (CSS) and overall survival (OS) was 40% and 36% for surgical cases and 35% and 26% for RT cases ( $p < 0.001$ ). In multivariate Cox model and propensity score analyses, there was no significant difference in CSS between surgery and RT (hazard ratio [HR] 0.99, 95% confidence interval [CI] 0.91-1.08); RT was associated with slightly inferior OS (HR 1.08, 95% CI 1.00-1.16).

## Conclusions

Survival of cystectomy patients in this contemporary population-based cohort is inferior to outcomes reported by higher volume, centres of excellence; radiotherapy results

are more consistent with previously reported outcomes. Our data suggest that in routine clinical practice there is a narrower gap in survival outcomes between treatment modalities, notwithstanding the difficulties of such comparisons in non-randomized, observational studies. We believe our data support the position that patients with muscle-invasive bladder cancer have a choice to make in definitive local management of this disease. We advocate that patients with MIBC would be best served by review within a multidisciplinary team.

### Use of perioperative chemotherapy

Since 1994, the use of NACT in Ontario has remained stable (mean 4%), while utilization of ACT increased over time, particularly for those with higher stage and node positive disease.<sup>23</sup> Despite the increased use of ACT, during the most recent study period (2004-2008) only 23% of patients with resected MIBC received any form of perioperative chemotherapy. There was wide geographic variation in referral to a medical oncologist before (range: 5%-40%) and after cystectomy (range: 26%-59%).<sup>26</sup> Utilization of ACT was associated with improved OS (HR 0.71, 95% CI 0.62-0.81) and CSS (HR 0.73, 95% CI 0.64-0.84).<sup>23</sup>

Cisplatin was used in 82% and carboplatin in 14% of treated patients.<sup>25</sup> In adjusted analyses, OS and CSS were lower among patients treated with carboplatin compared to those treated with cisplatin; OS HR 2.14 (95% CI 1.40-3.29) and CSS HR 2.06 (95% CI 1.26-3.37). Twenty-three percent of patients had ACT initiated >12 weeks after surgery and this delay was associated with inferior OS (HR 1.28, 95% CI 1.00-1.62) and CSS (HR 1.30, 95% CI 1.00-1.69).

### Conclusions

NACT remains substantially underutilized in routine clinical practice in Ontario, confirming similar rates across the rest of the country.<sup>8</sup> ACT is associated with a substantial survival benefit in the general population. Delaying ACT more than 12 weeks after cystectomy and substitution of carboplatin for cisplatin may lead to inferior outcomes. Lack of referral to a medical oncologist is an important barrier to use of NACT/ACT. Upstream decision-making by urologists to incorporate case review by a multidisciplinary team prior to cystectomy is an important target in future knowledge translation/educational initiatives.

### Quality of care delivered

Patients who had surgery at low volume hospitals (<4 cases/year) had inferior 5-year OS (27% vs. 35%,  $p < 0.01$ ) and CSS (31% vs. 38%,  $p < 0.01$ ) compared to higher volume

centres (>20 cases/year).<sup>27</sup> We observed a similar association with low volume surgeons (<2 cases/year); 5-year OS (28% vs. 36%,  $p < 0.01$ ) and CSS (31% vs. 39%,  $p < 0.01$ ) were inferior to outcomes with higher volume surgeons (>6 cases/year). In a multivariate analysis, both surgeon and hospital volumes were associated with CSS and OS. Short-term outcomes (30- and 90-day mortality) were also superior with higher volume providers. Although the adequacy of the lymph node dissection appeared to explain some of the effect, other key process of care (including perioperative chemotherapy) did not measurably explain the observed volume-outcome relationship.

### Conclusions

Higher provider volume in Ontario is associated with improved short- and long-term outcomes in the general population, solidifying results from other jurisdictions. During 1994 and 2008, half of patients in Ontario with MIBC had cystectomy by a surgeon who performed <2.5 cases/year. In many Canadian provinces thoracic and hepato-biliary surgery is already consolidated at designated centres; consideration should be given to centralizing cystectomy.

### Towards improved outcomes in the future

Clinical trials and practice guideline provide guidance regarding the delivery of care under optimal conditions. However, patients, providers and health systems in the “real world” can be very different from the tightly controlled context of a clinical trial. Population-based outcome studies provide insight into care and outcomes achieved in routine practice. They can also address issues that will not be answered in a clinical trial. Our recently completed population-based studies of bladder cancer in Ontario highlight that MIBC outcomes in routine practice are inferior compared to those reported in clinical trials. We add our voice to those who have identified some potentially remediable gaps in care.<sup>7,8,16</sup> Although more effective treatment regimens and accurate prognostic biomarkers to personalize care are attractive long-term goals, we propose that the time is right to re-focus efforts to improve the quality of the care delivered to patients with bladder cancer. Closing the efficacy-effectiveness gap through advocacy of true multidisciplinary care and consolidation of treatment with higher-volume providers is our best chance at measureable and timely progress for our patients.

**Competing interests:** Dr. Booth declares no competing financial or personal interests. Dr. Siemens is Editor-in-chief of *CUAJ*. Dr. Siemens holds investments in Janssen. He also is participating in clinical trials with Janssen, Amgen, Astellas and Ferring.

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**Correspondence:** Dr. Christopher Booth, Division of Cancer Care and Epidemiology, Queen's University Cancer Research Institute, 10 Stuart St., Kingston, ON K7L 3N6; boothc@kgk.kari.net