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Original article

# Concurrent chemoradiotherapy for bladder cancer: Practice patterns and outcomes in the general population

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ABSTRACT

*Background:* Clinical trials have shown that chemoradiotherapy (CRT) improves survival compared to radiation therapy (RT) alone in muscle-invasive bladder cancer. We describe uptake of CRT and comparative effectiveness in routine practice.

*Methods:* Electronic treatment records were linked to the population-based Ontario Cancer Registry to identify all patients with bladder cancer treated with curative-intent RT in 1999–2013. Modified Poisson regression was used to analyze factors associated with use of CRT. Cox model and propensity score analyses were used to explore factors associated with cancer-specific (CSS) and overall survival (OS).

*Results:* 1192 patients underwent RT during 1999–2013; median age was 79. Use of CRT increased over time: 36% (124/341) in 1999–2003, 38% (153/399) in 2004–2008, 48% (217/452) in 2009–2013 ($p$ = 0.001). Drug details were available for 82% (402/493) of CRT cases; the most common regimens were single-agent Cisplatin (57%, 230/402), single-agent Carboplatin (31%, 125/402) and 5-FU/Mitomycin (4%, 17/402). Factors associated with CRT include younger age ($p < 0.001$), lower comorbidity ($p$ = 0.001), and geographic region (range 14–89%, $p < 0.001$). Five year CSS and OS among CRT cases were 45% (95%CI 39–51%) and 35% (95%CI 30–40%). On adjusted analyses CRT was associated with superior survival compared to RT (CSS HR 0.70, 95%CI 0.59–0.84; OS HR 0.74, 95%CI 0.64–0.85); results were consistent on propensity score analysis. There was significant improvement in survival of all RT-treated cases (irrespective or chemotherapy delivery) in 2009–2013 compared to 1999–2003 (CSS HR 0.77, 95%CI 0.61–0.97; OS HR 0.82, 95%CI 0.69–0.98).

*Conclusion:* CRT is associated with superior survival compared to RT alone and its uptake corresponded to improved survival among all RT-treated cases in the general population. Uptake of CRT varies widely by geographic region.



Definitive treatment of muscle-invasive bladder cancer (MIBC) involves either radical cystectomy (RC) or curative-intent radiotherapy (RT). Due to a lack of Level I evidence, there is wide divergence in international guidelines and practice [1–4]. Available non-randomized data suggest that outcomes are comparable with the two approaches [5–7]. There is growing interest in concurrent chemoradiotherapy (CRT) as an alternative to RC.

Two randomized controlled trials (RCTs) have shown improved survival when chemotherapy is delivered concurrently with RT [8,9]. Promising outcomes with CRT have been reported from large single institution case series and a pooled analysis of RTOG phase I and phase II trials [6,10,11]. A recent study using the National Cancer Database described uptake and outcome of CRT among patients aged ≥80 years [12]. However, we are not aware of any studies that have reported uptake of CRT among all patients in routine practice. Population-based studies provide insight into management and outcomes among patients in the "real world" [13,14]. These studies can minimize sources of selection and referral bias that often limit single institution-based studies. To address this gap in the literature we undertook a population-based cohort study to (1) evaluate the uptake of CRT in the general population, and (2) describe outcomes achieved in routine practice.

## Methods

### *Study design and population*

This is a population-based, retrospective cohort study to describe management and outcome of muscle-invasive bladder

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cancer in the Canadian province of Ontario. Ontario has a population of approximately 13.5 million people and a single-payer universal health insurance program. All incident cases of bladder cancer in Ontario with urothelial carcinoma, adenocarcinoma, and squamous cell histology treated with RC or RT during 1999–2013 were included. The study population was classified into three temporal periods: 1999–2003, 2004–2008, 2009–2013. The study was approved by the Research Ethics Board of Queen's University, Kingston, Canada. This study was designed, analyzed, and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement [15,16].

### *Data sources*

The Ontario Cancer Registry (OCR) is a passive, population-based cancer registry that captures diagnostic and demographic information on at least 98% of all incident cases of cancer in the province of Ontario [17]. The OCR does not compile information about extent of disease or treatment. Indicators of the socioeconomic status (SES) of the community in which patients resided at diagnosis were linked as described previously [18]. A variety of electronic administrative health databases were linked to the OCR. Records of hospitalization from the Canadian Institute for Health Information (CIHI) provided information about surgical interventions; these records are known to be consistent and complete [19]. The clinical databases of Ontario's comprehensive cancer centers provided records of radiotherapy. These centers are the only providers of RT in the province and the electronic RT records are known to be 95% complete and 99% accurate with respect total dose, number of fractions, date of therapy, body region irradiated, and treatment intent [20]. Provincial physician billing records and treatment records from regional cancer centers were used to identify chemotherapy utilization.

### *Exposures and outcomes*

Comorbidity was classified using the Charlson Index modified for administrative data [21]. Regional variation was described at the level of Ontario's 14 Local Health Integration Networks. Cases treated with radical RT were identified from the treatment records of all RT centers. Cases treated to the bladder or pelvis were considered to be with curative intent if the physician-coded intent was "curative/radical" and the mean dose/fraction was $\leq$280 cGy/fraction. Cases with any record of chemotherapy delivered during the course of RT were classified as chemoradiotherapy. Chemotherapy delivered within 16 weeks prior to RT start was classified as neoadjuvant chemotherapy (NACT); chemotherapy delivered within 16 weeks after RT completion was defined as adjuvant chemotherapy (ACT). The primary outcome end-point was cancer-specific survival (CSS); this was prioritized over OS as it is less influenced by unmeasured comorbidity. To account for possible miscoding of cause of death, CSS included death from any cancer. Cystectomy-free survival (CFS) was defined as the time to first cystectomy or death from any cause. Vital status was available up to December 31, 2014 and cause of death was available from the OCR up to December 31, 2012.

### *Statistical analysis*

Comparisons of proportions between study groups were made using the Chi-square test; temporal trends were evaluated using the Cochran–Armitage test for trend. Survival was determined from start date of RT using the Kaplan–Meier method and comparisons between groups were made using the log-rank test. Factors associated with concurrent chemotherapy were evaluated by modified Poisson regression. Factors associated with CSS and OS were evaluated using the Cox proportional hazards regression model; we also conducted a propensity score analysis. The propensity score is the probability that a case would have CRT and it was modeled with observed confounding variables using a multivariable logistic regression model. Propensity scores allowed us to create five propensity strata with balanced confounding variables between CRT cases and RT cases. Survival of cases treated with CRT was compared to those treated with RT within each stratum using a Cox proportional hazards model; a summary HR combining the results across quintiles was calculated based on the stratified Cox's model [22,23]. Finally, to explore the extent to which uptake of CRT is associated with improved survival at the population level, we describe adjusted survival for all RT-treated cases (regardless of whether or not they received concurrent chemotherapy) across the study periods. Results were considered statistically significant at $p$-value < 0.05. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

## Results

### *Study population*

During 1999–2013, 1192 patients in Ontario with bladder cancer underwent curative-intent RT (Supplemental eFig. 1). As shown in Supplemental eFigs. 1 and 2, the vast majority (>75%) of patients treated with curative intent in Ontario undergo cystectomy and not radical RT. Moreover, substantially more patients with bladder cancer are treated with palliative-intent RT rather than curative-intent RT. Over the three study periods, the proportion of patients treated with radical RT and radical cystectomy has remained stable (Supplemental eFig. 2). Chemoradiotherapy was delivered to 41% (494/1192) of cases; NACT and ACT were delivered to 12% (146/1192) and 7% (83/1192) of cases, respectively. Median age was 79 years and 76% of patients were male (Table 1). During the study period, age (34% of cases 1999–2003 were 80+ years vs 51% of cases in 2009–2013, $p < 0.001$) and comorbidity (10% of cases 1999–2004 had a Charlson score of 3+ vs 18% of cases in 2009–2013, $p = 0.042$) increased among all patients treated with RT (Supplemental eTable 1).

### *Delivery of RT and CRT*

Most patients treated with RT (694/1192 58%) received >60 Gy over 30+ fractions (Supplemental eFig. 3). Dose/fractionation of RT delivery was slightly lower among patients treated with RT alone compared to those treated with CRT (56% vs 62% received >60 Gy over 30+ fractions, $p = 0.051$) (Supplemental eFig. 4). Dose/fractionation of RT delivery was comparable across study periods (63% 1999–2003, 51% 2004–2008, 61% 2009–2013 received >60 Gy over 30+ fractions, $p < 0.001$) (Supplemental eFig. 5).

There was substantial uptake of CRT over time with the largest change in practice between 2003–2008 and 2009–2013. CRT rates were 36% (124/341) in 1999–2003, 38% (153/399) in 2003–2008, and 48% (217/452) in 2009–2013 ($p = 0.001$). Further adoption of CRT was observed within the most recent study period (from 44% in 2009 to 57% in 2013, $p = 0.036$) (Fig. 1). Chemotherapy dose/regimen data were available for 82% (402/493) of CRT cases. The most common regimens were single agent cisplatin (57%, 230/402), carboplatin (31%, 125/402) and 5FU-mitomycin (4%, 17/402).

Adjusted analyses show that patients with advanced age (RR age 80+ vs 20–59 years 0.40 95%CI 0.32–0.51) and greater comorbidity (RR Charlson 1+ vs 0 0.81 95% CI 0.71–0.91) were less likely to receive CRT (Table 2). CRT utilization rates varied dramatically across regions (from 14% to 91%, $p < 0.001$).

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