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Original article

Perioperative chemotherapy for bladder cancer in the general population: Are practice patterns finally changing?

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Abstract

Background: Uptake of perioperative chemotherapy for muscle-invasive bladder cancer (MIBC) has been historically poor. We describe contemporary use of neoadjuvant (NACT) and adjuvant chemotherapy (ACT) as well as medical oncology (MO) referral patterns in routine practice.

Methods: Electronic treatment records were linked to the population-based Ontario Cancer Registry to identify all MIBC patients treated with cystectomy in Ontario 1994 to 2013. Physician billing records were used to identify consultation with MO. Practice patterns in the contemporary era (2009–2013) are compared with data from 1994 to 2008.

Results: A total of 5,582 patients had cystectomy for MIBC. Use of NACT increased from 4% in 1994 to 2008 to 19% in 2009 to 2013 ($P < 0.001$); rates continued to rise in the most recent era from 12% in 2009 to 27% in 2013 ($P < 0.001$). ACT was delivered to 20% of patients in 2009 to 2013 (19% in 1994–2008, $P = 0.875$). Use of any chemotherapy (NACT or ACT) in 2009 to 2013 was 35% compared to 23% in 1994 to 2008 ($P < 0.001$). Preoperative referral rates during 2009 to 2013 to MO were greater than 1994 to 2008 (32% vs. 11%, $P < 0.001$); referral rates continued to increase in recent years from 21% in 2009 to 44% in 2013 ($P < 0.001$). The proportion of referred patients ultimately treated with NACT increased substantially; from 32% in 1994 to 1998 to 54% in 2009 to 2013 ($P < 0.001$).

Conclusions: After many years of practice lagging behind evidence, use of NACT in the general population has increased substantially. Our results suggest that increased uptake has been driven by greater preoperative referral to MO as well as greater propensity of MOs to treat referred patients.

Keywords: Bladder cancer; Chemotherapy; Cystectomy; Quality of care; Multidisciplinary care; Knowledge translation

1. Introduction

Muscle-invasive bladder cancer (MIBC) may be locally controlled by cystectomy or radiotherapy but more than 50% of patients ultimately die of distant metastases. International guidelines recommend neoadjuvant chemotherapy (NACT) on the basis of level I evidence [1–3]. Although less robust than NACT, there is growing evidence to suggest that adjuvant chemotherapy (ACT) might offer a comparable benefit to NACT [4]. In this context, practice recent guidelines are now shifting to recommend either NACT or ACT for MIBC [2].

Despite the pivotal randomized controlled trials in 1999 and 2003 [5,6], multiple studies showed minimal uptake of

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NACT and a paradoxical greater uptake of ACT [7–9]. These initial studies reported practice in the 1990s and mid-2000s. We have previously reported practice patterns in the Canadian province of Ontario during 1994 to 2008 and showed that use of NACT was very low (mean utilization rate 4%) with no clear increase over time [10]. Despite multiple studies describing low use of perioperative chemotherapy, potential reasons for underutilization are not well described. Potential reasons include low referral rate from urology to medical oncology (MO), patient ineligibility owing to renal dysfunction, and patient/physician preference against chemotherapy [11]. Our data showed that during 1994 to 2008 only 10% of patients with MIBC were referred to MO before cystectomy [12]. Recent surveys suggest that physician attitude towards chemotherapy for bladder cancer may be changing [13,14], and 2 population-based studies have described increasing use of chemotherapy [15,16]. There remains a paucity of data to describe to what extent MO referral rates have changed over time. We undertook the following study to provide insight into delivery of perioperative chemotherapy and referral patterns to MO in the contemporary era.

2. Methods

2.1. Study design and population

This is a population-based, retrospective cohort study to describe use of perioperative chemotherapy and referral to MO among patients with MIBC in the Canadian province of Ontario. We have previously reported practice patterns during 1994 to 2008 [10,12]; in this report we update this analysis to include patients treated in 2009 to 2013. 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 who underwent cystectomy from 1994 to 2013 were identified using the Ontario Cancer Registry (OCR) and linked treatment records. Stage of disease was not routinely available in the existing data sources; for this reason we obtained surgical pathology reports for all cystectomy cases. Patients with muscle-invasive urothelial cancer as per the cystectomy pathology report were included. Patients with T0/T1 disease at cystectomy who were treated with preoperative chemotherapy or radiation were not excluded; these cases very likely had MIBC at the time of diagnosis but were subsequently downstaged. The primary study objective was to describe practice patterns and factors associated with use of perioperative chemotherapy in the general population. The secondary objective was to describe referral rates to MO. The study was approved by the Research Ethics Board of Queen's University.

2.2. Data sources

The 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 also provides information about vital status and cause of death. Records from the Canadian Institute for Health Information (CIHI) provided information about surgical procedures. Provincial chemotherapy and physician billing records were used to identify chemotherapy use. Pathology reports were obtained from the OCR. A team of trained data abstractors reviewed the pathology reports and entered information about extent of disease and surgical procedure into an electronic database.

2.3. Measures and outcomes

Indicators of the socioeconomic status (SES) of the community in which patients resided at time of diagnosis were linked to the OCR as described previously to create SES quintiles [18]. Geographic regions were assigned based on patient postal code and boundaries of local health integration networks. Comorbidity was classified using the modified Charlson index [19]. Each case was assigned a hospital and surgeon volume index as previously described [20].

There is no data source that allows identification of medical oncologists in Ontario. Accordingly, as a proxy measure of medical oncologists we identified the 286 physicians who submitted billing records for MIBC NACT or ACT in 1994 to 2013. We have used a similar approach elsewhere [21–23]. Each case was considered to have been seen by a medical oncologist if any of these physicians submitted visit billing codes for that patient within 16 weeks before or after surgery. NACT was defined as any chemotherapy administered within 16 weeks before surgery. ACT was defined as any chemotherapy administered within 16 weeks after surgery.

2.4. Statistical analysis

Comparisons of proportions between study groups and across the study period were made using the chi-square test and the Cochran-Armitage test for trend, respectively. To describe temporal trends we created subgroups of patients based on year of cystectomy: 1994 to 1998, 1999 to 2003, 2004 to 2008, and 2009 to 2013. Factors associated with chemotherapy use and referral to MO were evaluated by logistic regression. Analyses related to postoperative MO referral and ACT use were restricted to those cases who did not have NACT or preoperative radiotherapy since pathologic findings at time of cystectomy would not accurately reflect extent of disease.

To explore the extent to which provider-level variation explains differences in practice, we undertook 2 exploratory analyses of patients treated in the most contemporary study period (2009–2013). We applied the fitted regression model (for patient and disease-level factors associated with use of NACT/ACT among patients referred to MO) to patients not referred to MO to compute their predicted probability of getting NACT had they been referred to MO. To explore