Radical Cystectomy and Adjuvant Chemotherapy for Bladder Cancer in the Elderly: A Population-based Study

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OBJECTIVE To assess radical cystectomy (RC) outcomes and adjuvant chemotherapy (ACT) use in the elderly in routine practice. Bladder cancer occurs most commonly in the elderly. RC, standard treatment for muscle-invasive bladder cancer, presents challenges in older patients. Suboptimal evidence guides ACT use.

METHODS All patients undergoing RC for urothelial cancer in Ontario from 1994 to 2008 were identified using the Ontario Cancer Registry. Pathology reports and treatment records were linked to the database. Patients were age stratified as <70, 70-74, 75-79 and ≥80 years. Logistic regression and Cox proportional hazards identified associations with and effectiveness of ACT use.

RESULTS We identified 3320 patients: 1362 (41%) aged <70 years; 674 (20%) aged 70-74 years; 674 (19%) aged 75-79 years, and 657 (20%) aged ≥80 years. Thirty-day (1%, 2%, 2%, 6%; P <.0001) and 90-day (5%, 8%, 9%, 15%; P <.0001) mortality increased with age. Age-stratified 5-year cancer-specific survival was 42%, 37%, 34%, and 32%, respectively (P <.001); 5-year overall survival was 40%, 34%, 28%, and 23%, respectively (P <.001). ACT decreased with age (27%, 16%, 12%, 5%; P <.0001). Among ACT patients, 87% aged <70 years received cisplatin vs 73% aged ≥70 years (P = .003). ACT was associated with improved cancer-specific survival (hazard ratio [HR] = 0.73 and 95% confidence interval [CI] = 0.59-0.89 for age <70 years and HR = 0.73 [95% CI = 0.59-0.89] for ≥70 years) and overall survival (HR = 0.70 [95% CI = 0.58-0.85] for age <70 years and HR = 0.70 [95% CI = 0.59-0.84] for ≥70 years) across all age groups.

CONCLUSION Cystectomy carries a higher risk of postoperative mortality in elderly patients in routine clinical practice. ACT is used infrequently in older patients despite a substantial survival benefit observed across all age groups. UROLOGY 85: 791–798, 2015. © 2015 Elsevier Inc.

Bladder cancer is primarily a disease of the elderly; 71% of patients are diagnosed after the age of 65 years.[1] Radical cystectomy (RC) with regional lymphadenectomy and urinary diversion remains a part of standard management of muscle-invasive urothelial carcinoma of the bladder.[2]

Studies addressing mortality and morbidity of RC in the elderly report mixed results. A large single-institution study revealed no differences in perioperative survival or complication rates in patients aged >80 years.[3] A multi-institutional study of 888 consecutive RC patients, however, found worse pathologic and disease-specific outcomes in patients aged >80 years, and a collaborative review corroborated higher morbidity and mortality in elderly patients.[4,5] Elderly patients are more likely to suffer comorbidities and frailty that might disqualify them from surgery or increase the risk of complications, as evidenced in the Surveillance, Epidemiology, and End Results program and in systematic reviews.[5,6] In addition, perioperative chemotherapy is used less frequently in elderly patients, including those with muscle-invasive disease.[4,6-9]

Much of the data describing radical treatment and outcomes of urothelial carcinoma of the bladder (UCB) are based on case series from high-volume tertiary centers. We hypothesized that surgical and survival outcomes

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would be worse, and the use of adjuvant chemotherapy (ACT) lower, in elderly patients; we sought to investigate the use of ACT and short- and long-term outcomes of elderly patients with UCB in the general population.

METHODS

Study Design and Population

This is a report of a population-based, retrospective cohort study of all patients with bladder cancer treated with cystectomy in the Canadian province of Ontario. Primary results have been previously reported.[9] Ontario has a single-payer universal health insurance program that covers a population of approximately 13.5 million. All incident patients in Ontario who underwent cystectomy for urothelial carcinoma between 1994 and 2008 were identified using the Ontario Cancer Registry (OCR) and linked treatment records. Surgical pathology reports were obtained for all patients. The primary objective of this study was to describe surgical practices and outcomes among elderly patients treated with RC for UCB in the general population. We also assessed the use of ACT for muscle-invasive urothelial cancer in general practice. The Research Ethics Board of Queen's University approved the study.

Data Sources

The OCR captures diagnostic and demographic information on at least 98% of all incident cases of cancer diagnosed in the province of Ontario.[10] Vital status was available up to December 31, 2010, and cause of death was available up to December 31, 2008. Socioeconomic status of the community in which patients resided at the time of diagnosis, based on the median household income from the 2001 census within their postal code of residence, was linked to the OCR and divided into quintiles (Q) of median household income as compared to the entire province.[11] Q1 represents the lowest 20% of the Ontario population. Hospitalization records obtained from the Canadian Institute for Health Information included surgical interventions, length of stay (LOS), and subsequent admissions to hospital. Hospital participation in collection of records is consistent and complete throughout Ontario.[12] The use of chemotherapy was identified through provincial physician billing records and treatment records from Ontario's regional cancer centers. Surgical pathology reports were obtained from the OCR.

Definitions of Comorbidity and Management

The study population was classified by age (<70 years, 70-74 years, 75-79 years, >80 years). Comorbidity was classified using the modified Charlson index on the basis of all the non-cancer diagnoses recorded during any hospital admission within 5 years before surgery.[13,14] Neoadjuvant chemotherapy (NACT) was defined as any chemotherapy administered within 16 weeks before surgery. Adjuvant chemotherapy (ACT) was defined as any chemotherapy administered within 16 weeks after surgery.

Outcome Measures

The primary outcome end point was cancer-specific survival (CSS), censored as of December 2008. To account for possible cause of death miscoding, CSS included death from any cancer. CSS was prioritized over overall survival (OS) as it was felt likely to be less vulnerable to bias from unmeasured prognostic factors. Secondary outcome measures included 5-year OS (censored as of December 2010) and postoperative mortality at 30 and 90 days.

Statistical Analysis

Survival was determined from date of surgery using the Kaplan-Meier technique, and comparisons between groups were made using the log rank test. Factors associated with postoperative mortality and use of ACT were evaluated by logistic regression. The associations between patient-, disease-, and treatment-related factors with OS or CSS were evaluated using Cox proportional hazards regression. To evaluate the association between ACT and survival, we undertook a stratified analysis (elderly patients vs nonelderly patients) while controlling for other significant prognostic factors. Patients that received NACT or preoperative radiotherapy (<5%) were excluded from the analysis of survival because information about pathologic stage for these patients would be less reliable. Hospital readmission rates at 30 and 90 days were derived using all patients, including those who died in hospital and those who remained in hospital at 30 and 90 days. Study results were considered statistically significant at a P value <.05. As per Ontario Institute for Clinical and Evaluative Science's policy, small cells (1-5 patients) are not reported. All analyses were performed using SAS, version 9.1 (SAS Institute, Cary, NC).

RESULTS

Study Population

We identified 3320 patients who underwent RC for UCB in Ontario between 1994 and 2008, of whom 1958 (59%) were aged >70 years. Patient- and disease-related data across age strata are listed in Table 1. Over the study period, the proportion of patients aged ≥80 years increased (17% during 1994-1998, 19% during 1999-2003, and 22% during 2004-2008; $P = .002$). Elderly patients had greater comorbidity ($P < .001$) and more extensive disease (ie, T3/4 tumors; $P = .002$) than younger patients ($P < .001$). Patients aged >70 years were more likely to have pathologic node stage NX ($P < .001$), an indication of the absence of lymphadenectomy at the time of RC. Among the 1958 patients aged >70 years, 1701 (87%) had muscle-invasive urothelial cancer.

Practice Patterns

Details related to treatment are listed in Supplementary Table 1. Elderly patients were less likely to have surgery at a regional cancer center ($P = .002$) and less likely to be treated with NACT or ACT ($P < .001$). Perioperative chemotherapy regimens also differed across age groups on the basis of data available for 257 patients. Cisplatin was used in 144 of 165 patients (87%) aged <70 years and in 67 of 92 (73%) aged >70 years; carboplatin was used in 15 of 165 (9%) and 21 of 92 (23%) of cases, respectively ($P = .009$).

Factors associated with receiving ACT among 1701 patients aged >70 years with muscle-invasive cancers are presented in Table 2. Younger age ($P < .001$), higher socioeconomic status ($P = .007$), lower Charlson comorbidity score ($P = .021$), and unknown or positive lymph nodes ($P < .001$) were independently associated