VALUE IN HEALTH 16 (2013) 610–618

Available online at www.sciencedirect.com

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Radical Cystectomy versus Bladder-Preserving Therapy for Muscle-Invasive Urothelial Carcinoma: Examining Confounding and Misclassification Biasin Cancer Observational Comparative Effectiveness Research

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ABSTRACT

Objectives: Radical cystectomy (RC) is the standard treatment for muscle-invasive urothelial carcinoma of the bladder. Trimodality bladder-preserving therapy (BPT) is an alternative to RC, but randomized comparisons of RC versus BPT have proven infeasible. To compare RC versus BPT, we undertook an observational cohort study using registry and administrative claims data from the Surveillance, Epidemiology and End Results-Medicare database. **Methods:** We identified patients age 65 years or older diagnosed between 1995 and 2005 who received RC (n = 1426) or BPT (n = 417). We examined confounding and stage misclassification in the comparison of RC and BPT by using multivariable adjustment, propensity score–based adjustment, instrumental variable (IV) analysis, and simulations. **Results:** Patients who received BPT were older and more likely to have comorbid disease. After propensity score adjustment, BPT was associated with an increased hazard of death from any cause (hazard ratio [HR] 1.26; 95% confidence interval [CI] 1.05–1.53) and from bladder cancer (HR 1.31; 95% CI 0.97–1.77). Using the local area cystectomy rate as an instrument, IV analysis demonstrated no differences in survival between BPT and RC (death from any cause HR 1.06; 95% CI 0.78–1.31; death from bladder cancer HR 0.94; 95% CI 0.55–1.18). Simulation studies for stage misclassification yielded results consistent with the IV analysis. **Conclusions:** Survival estimates in an observational cohort of patients who underwent RC versus BPT differ by analytic method. Multivariable and propensity score adjustment revealed greater mortality associated with BPT relative to RC, while IV analysis and simulation studies suggest that the two treatments are associated with similar survival outcomes.

Keywords: chemotherapy, comparative effectiveness research, cystectomy, radiotherapy, SEER Program, urinary bladder neoplasms.

Introduction

Urothelial carcinoma of the bladder (UCB) affects more than 70,000 people annually in the United States, the majority of whom are elderly, and accounts for nearly 5% of the total cost of cancer care to Medicare. A substantial portion of patients present with or progress to muscle-invasive UCB, an aggressive cancer associated with a high risk of death from metastatic disease.

Radical cystectomy (RC) is the guideline-recommended standard treatment for muscle-invasive UCB and involves removal of the bladder and prostate for men and anterior exenteration (including the bladder, uterus, ovaries, and part of the vagina) for women. Bladder-preserving therapy (BPT), a curative treatment regimen composed of transurethral resection (TUR) of the bladder tumor, radiotherapy, and chemotherapy, presents a compelling alternative to RC because long-term studies have shown that the majority of BPT patients retain good bladder function [1,2]. Yet, concerns about reduced survival without radical surgery remain and randomized comparisons of RC to BPT have proven infeasible.

Nonrandomized studies of RC versus BPT suffer from two sources of bias that threaten validity in observational cancer

Presented in part at the American Society for Radiation Oncology Annual Meeting, Miami, FL, October 2011.

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1098-3015/$36.00 – see front matter

http://dx.doi.org/10.1016/j.jval.2013.01.005

comparative effectiveness research (CER): confounding and misclassification. Confounding occurs when measured or unmeasured differences between patients are related to both the exposure (e.g., treatment assignment) and outcome in a way that creates a false association; for example, patients receiving cystectomy tend to be younger, have fewer comorbidities, and have better performance status. Cancer registry data sets, often used for observational cancer CER, capture variables for patient age and comorbidities, but do not report performance status, an important unmeasured confounder.

Adjustment for measured confounding depends on the ability to accurately observe possible confounding variables. Cancer registry data sets may mischaracterize important confounding variables; controlling for such variables may exacerbate rather than reduce bias. For patients with UCB, those who undergo RC have pathologic staging while those who undergo BPT have clinical staging. Clinical stage is based on available information obtained prior to cystectomy, including bimanual physical examination, imaging, and cystoscopy. Pathologic staging adds additional information obtained from microscopic examination of the bladder specimen after cystectomy. Discordance between clinical and pathological stage induces bias in the comparison of RC to BPT because clinical staging is more likely to underestimate muscle invasion, a pathologic finding that is associated with worse survival outcomes [3].

We conducted this study to evaluate differences in survival in the comparison of RC to BPT using traditional multivariable regression and propensity score adjustment, which adjust for measured confounding, and instrumental variable (IV) analyses, which theoretically account for both measured and unmeasured confounding. Our secondary aim was to examine the sensitivity of traditional regression survival estimates to stage misclassification through simulation.

Methods

Study Design

The study was a retrospective, observational cohort study using registry and administrative claims data from the Surveillance, Epidemiology and End Results (SEER)-Medicare database. This research was approved by the institutional review board.

Data Sources

The SEER-Medicare database links patient demographic and tumor-specific data collected by SEER cancer registries to Medicare claims for inpatient and outpatient care. To obtain information on physicians and hospitals, Medicare claims were merged with the Medicare Physician Identification and Eligibility Record and the SEER-Medicare hospital file. To explore candidate instruments, we grouped patients into hospital referral regions (HRRs) defined by the Dartmouth Atlas of Health Care. HRRs represent regional health care markets for tertiary medical care.

Study Population

We identified 54,402 patients with UCB age 65 years or older diagnosed between January 1, 1995, and December 31, 2005, in SEER with follow-up through December 31, 2008, in Medicare. To assign patients to therapy during the 6-month period after diagnosis, we excluded 12,801 patients enrolled in a health maintenance organization and 2,890 patients not enrolled in the fee-for-service Part B Medicare program (health care claims may not be submitted for such patients). We identified 6,486 patients with muscle-invasive (stages 2 and 3) UCB after excluding patients who were not staged (n = 2,866), stage 0 (19,206), stage 1 (8,796), and stage 4 (1,357).

To define the primary analytic cohort eligible for either RC or BPT, we made the following additional exclusions: RC with chemotherapy or radiotherapy (401), radiotherapy with non–platinum-based chemotherapy (166), palliative treatment with chemotherapy alone, radiotherapy alone, or expectant management (combined 3843), nonconcurrent chemoradiotherapy (e.g., administered > 3 months apart, 54), absent Medicare codes for initial TUR (64), HRRs with 10 or fewer patients over the study period (50), and unknown race [2]. To avoid survivorship bias, we excluded patients who died within 3 months of diagnosis (n = 71; RC is associated with perioperative mortality while BPT required that patients "survive" to receive trimodality therapy). The primary analytic cohort was composed of 1426 RC and 417 BPT patients.

Definition of Variables

RC and BPT were assigned on the basis of identification from Medicare inpatient, outpatient, and physician/supplier component files using *International Classification of Diseases, Ninth Revision* and Common Procedure Terminology/Healthcare Common Procedure Coding System (CPT/HCPCS) [4–6]. RC was defined as complete cystectomy with or without pelvic lymph node dissection or pelvic exenteration. BPT was defined as consisting of TUR of the bladder tumor, concurrent platinum-based chemotherapy, and radiotherapy.

Patient characteristics included age, gender, race, ethnicity, marital status, tumor grade, and comorbid disease. Comorbidities were identified by classifying all available inpatient and outpatient Medicare claims for the 12-month interval preceding UCB diagnosis into 46 categories [7]. We staged patients' cancer according to American Joint Committee on Cancer Staging Manual, 6th edition, using SEER variables for disease extent. SEER registries collect pathologic staging for RC patients and clinical staging for nonsurgical patients. Physician and hospital characteristics served as proxies for volume, experience, and practice style. Physician characteristics included years in practice (from medical school graduation), and hospital characteristics included number of beds and academic affiliation. Patients were assigned to urologists and hospitals on the basis of identifiers associated with TUR billing claims. Contextual variables included year of diagnosis, registry, population of county of residence, and median household income in census tract of residence (US $, obtained from the Patient Entitlement and Diagnosis Summary File provided with SEER-Medicare data).

The primary outcomes were time to death from any cause and time to death from bladder cancer. Underlying cause of death was determined from SEER records. The observation time for follow-up was calculated as the time from either cystectomy or the start date of radio- or chemotherapy until the Medicare date of death or end of follow-up (December 31, 2008). In the analysis of death from bladder cancer, patients who died from a cause other than bladder cancer were also censored at the Medicare date of death.

Statistical Analysis

We assessed covariate imbalances between treatment groups by using chi-square statistics and *t* tests. The Kaplan-Meier method was used to compare estimates of unadjusted overall survival and bladder cancer–specific survival. For multivariable adjustment, patient, demographic, and physician/hospital variables were included in the multivariable model, except for tumor stage [8]. We excluded stage from our primary analyses of confounding in multivariable, propensity score, and IV models and addressed