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Original article

The effect of metformin on cancer-specific survival outcomes in diabetic patients undergoing radical cystectomy for urothelial carcinoma of the bladder

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Abstract

Purpose: Metformin, a first-line oral therapy for diabetes, has anticancer properties. Our objective was to evaluate the association between metformin use and oncologic outcomes in diabetic patients undergoing radical cystectomy (RC) for bladder cancer (BC).

Methods: A single-institution retrospective cohort (January 1997–June 2013) of diabetic patients undergoing RC was assembled. Medication use was assessed at time of surgery. Outcome measures were recurrence-free survival (RFS), BC-specific survival (BCSS), and overall survival (OS). Multivariable Cox proportional hazards models were used. To create parsimonious models, the change of estimate approach (10% threshold) was used as a variable selection strategy for final model inclusion separately for each outcome measure.

Results: Of 421 patients, 85 (20%) had diabetes. There were 39 (46%) patients on metformin therapy. Among diabetic patients, there were 21 patients with BC recurrence, 16 who died of BC, and 30 who died overall. In univariate analyses, metformin use among diabetic patients was associated with improved RFS (hazard ratio = 0.54, 95% CI: 0.33–0.88, $P = 0.013$) and trended toward improved BCSS (hazard ratio = 0.65, 95% CI: 0.40–1.07, $P = 0.087$), but not with OS ($P = 0.87$). In multivariable models, metformin use among diabetic patients was associated with significantly improved RFS (adjusted hazard ratio = 0.38, 95% CI: 0.20–0.72, $P = 0.003$) and BCSS (adjusted hazard ratio = 0.57, 95% CI: 0.35–0.91, $P = 0.019$), but not with OS ($P = 0.89$). Use of other oral hypoglycemic agents or insulin was not associated with oncologic outcomes.

Conclusions: Our study is among the first to report an association between metformin use and improved RFS and BCSS in diabetic patients undergoing RC. Given its low cost and demonstrated safety among nondiabetic patients, further studies are warranted to evaluate potential therapeutic and preventive roles of metformin in BC.

Keywords: Cystectomy; Mortality; Patient outcome assessment; Urinary bladder neoplasms; Metformin

1. Introduction

Bladder cancer (BC) is the second most common genitourinary malignancy and is expected to account for 74,690 new cancer cases and 15,580 cancer deaths in 2014 in the United States [1]. Radical cystectomy (RC) with lymphadenectomy is the mainstay of therapy in the

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management of both muscle-invasive bladder cancer (MIBC) and high-risk non–muscle-invasive bladder cancer (NMIBC) [2,3]. Despite surgery, many patients develop recurrence of disease and eventually die of their cancer [4].

Metformin is a member of the biguanide medication class and is used primarily to treat type 2 diabetes. Recently, metformin has gained interest for its antineoplastic properties against prostate [5,6], pancreatic [7], colorectal [8,9], endometrial [10], ovarian [11,12], renal [13], oral [14], gastric [15], and breast [16] cancers. In vitro and animal models have demonstrated antineoplastic effects of metformin on BC as well [17]; however, presently there are only limited clinical data on the influence of metformin use in patients with BC [18,19].

Our objective was to evaluate the association between metformin use and oncologic outcomes in diabetic patients undergoing RC for BC. Given the antineoplastic effects of metformin, our hypothesis was that metformin use would be associated with improved recurrence-free survival (RFS), BC-specific survival (BCSS), and overall survival (OS) when compared with nonusers.

2. Methods

2.1. Patients and data sources

After obtaining institutional research ethics board approval, patients who underwent RC between January 1997 and June 2013 were identified retrospectively using our institutional database (University Health Network, Toronto). Patients with a diagnosis of diabetes were identified and included if they had MIBC, T1 high-grade disease, Bacilli Calmette-Guérin–refractory carcinoma in situ, or recurrent Ta disease that was endoscopically uncontrollable and underwent RC as primary treatment with curative intent. Patients were excluded if RC was performed for salvage following failed chemoradiation bladder-preserving therapy, consolidation of nonlocalized disease following response to primary chemotherapy, invasive prostatic urothelial carcinoma, or palliation in the context of metastatic disease.

Clinical parameters were ascertained using electronic medical record review. Use of metformin, any other oral hypoglycemics, and insulin was assessed at the time of surgery. Given the infrequent use of oral hypoglycemics other than metformin, these medications were combined into a single category. Mortality data, including cause of death, was obtained through electronic medical record review and the Princess Margaret Hospital Cancer Registry (which obtains data from the Ontario Cancer Registry, a population-based provincial registry that collects data from various sources for all Ontario residents diagnosed with cancer, including their death certificates) [20].

2.2. Outcome measures

The outcome measures were RFS, BCSS, and OS. These outcomes were measured from the date of RC, or the date of initiation of chemotherapy for patients who received neoadjuvant chemotherapy (NAC). Disease relapse was defined as imaging, cystoscopic, or physical examination evidence of disease recurrence. For each outcome, patients were censored at the date of last follow-up or the date at which another outcome had occurred.

2.3. Statistical analysis

Statistical analyses were performed using SAS v9.3 (SAS Institute Inc., Cary, NC). Baseline characteristics were compared between metformin users and nonusers using the *t* test or Wilcoxon rank sum test for continuous variables and the chi-squared or the Fisher exact tests for categorical variables. Event rates were calculated for BC recurrence, BC-specific mortality, and overall mortality per 1,000 person-years and were compared between metformin users and nonusers. Stratified analyses were performed based on use of other diabetes medications. Kaplan-Meier techniques were used to estimate survival distributions for each of the previously described outcome measures, and log-rank tests were used to compare the survival distributions between the metformin and the nonmetformin groups.

Factors associated with OS, BCSS, and RFS were assessed using univariate and multivariable Cox proportional hazards models. The following parameters were considered for inclusion in multivariable models: patient-related risk factors (age at baseline, gender, and Charlson comorbidity index), presence of extravesical disease (T3/4 or N+), treatment-related parameters (use of NAC, use of adjuvant chemotherapy [AC], and surgical margin status), and diabetes treatment regimen (metformin, other oral hypoglycemics, or insulin). Charlson score was log transformed to improve model fit. AC was operationalized as a time-varying covariate to address immortal time bias [21]. Clustering of outcomes by surgeon was accounted for by using a robust sandwich covariance matrix estimator [22].

To create parsimonious models, the change of estimate approach was used as the variable selection strategy for each outcome measure to avoid overspecified models. With this strategy, the effect of separately adding each putative confounder on the hazard ratio (HR) estimate of the main exposure (metformin use) is assessed [23]. Only covariates altering the HR of the exposure by at least 10% (i.e., operational confounders) were retained, whereas those that did not were excluded from the final model. Notably, for a variable to be a confounder, it must be associated with both the exposure and the outcome. Therefore, even important predictors of outcomes were not confounders if they were not differently distributed between exposure groups, and as such, it was not necessary to include such variables in our final models, as they did not meaningfully change the HR estimate of the association between the main exposure of interest and the outcome. An exception in our study was stage, which was retained in all models because of its clinical importance. This strategy allowed us to minimize the number of variables in our models, in the context of a small cohort and limited number of