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ORIGINAL REPORT

Risk of Fracture After Radical Cystectomy and Urinary Diversion for Bladder Cancer

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ABSTRACT

Purpose
Radical cystectomy and urinary diversion may cause chronic metabolic acidosis, leading to long-term bone loss in patients with bladder cancer. However, the risk of fractures after radical cystectomy has not been defined. We assessed whether radical cystectomy and intestinal urinary diversion are associated with increased risk of fracture.

Patients and Methods
Population-based study using SEER-Medicare–linked data from 2000 through 2007 for patients with stage 0-III bladder cancer. We evaluated the association between radical cystectomy and risk of fracture at any site, controlling for patient and disease characteristics.

Results
The cohort included 50,520 patients, of whom 4,878 had cystectomy and urinary diversion. The incidence of fracture in the cystectomy group was 6.55 fractures per 100 person-years, compared with 6.39 fractures per 100 person-years in those without cystectomy. Cystectomy was associated with a 21% greater risk of fracture (adjusted hazard ratio, 1.21; 95% CI, 1.10 to 1.32) compared with no cystectomy, controlling for patient and disease characteristics. There was no evidence of an interaction between radical cystectomy and age, sex, comorbidity score, or cancer stage.

Conclusion
Patients with bladder cancer who have radical cystectomy and urinary diversion are at increased risk of fracture.

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INTRODUCTION

Bladder cancer is the fourth most common cancer and the eighth leading cause of cancer death in men in the United States.[1] It is estimated that, in 2013, more than 54,000 men and almost 18,000 women were diagnosed with bladder cancer and more than 15,000 died as a result of this disease.[2] Radical cystectomy with urinary diversion and bladder-sparing multimodality therapy are the primary treatment options for patients with nonmetastatic muscle-invasive bladder cancer. After cystectomy, urine is diverted, and the urinary tract reconstructed using an intestinal segment such as the ileum.

Urinary diversions are either incontinent (such as an ileal conduit) or continent (catheterizable pouch or neobladder). Although a variety of intestinal segments may be used, ileum is the most commonly used because of anatomic advantages and the lower rate of metabolic and surgical complications. Intestinal segments are also used for urinary tract reconstruction for other conditions, such as augmentation cystoplasty for neurogenic bladder, ileal ureter for ureteral reconstruction, and urinary diversion after cystectomy for benign conditions.

The long-term metabolic consequences of intestinal urinary diversions are unknown. On exposure to urine, ileum reabsorbs ammonium and chloride and excretes bicarbonate. This impairs acid elimination and results in chronic metabolic acidosis in up to 70% of patients with intestinal urinary diversions.[3-5] In response to metabolic acidosis, bone buffers the excess protons and releases calcium, resulting in hypercalciuria, without a concomitant increase in intestinal calcium absorption.[6,7] Chronic metabolic acidosis also inhibits osteoblast activity, stimulates osteoclast bone resorption, inhibits renal tubular calcium reabsorption, causes hypophosphatemia through renal phosphate wasting and leads to negative calcium

Table 1. Characteristics of Cohort by Cystectomy Status

Characteristic	All Patients	Cystectomy		No Cystectomy		*P*
		No.	%	No.	%	
Total	50,520	4,878	10	45,642	90	
Age at diagnosis, years						
66-69	7,069	1,000	21	6,069	13	< .001
70-74	11,003	1,446	30	9,557	21	
75-79	12,652	1,369	28	11,283	25	
≥ 80	19,796	1,063	22	18,733	41	
Sex						
Male	37,633	3,611	74	34,022	75	NS
Female	12,887	1,267	26	11,620	25	
Race						
White	46,445	4,477	92	41,968	92	NS
Black	1,963	178	4	1,785	4	
Hispanic	572	67	1	505	1	
Other	1,540	156	3	1384	3	
Census tract median income						
1st quartile	11,765	1,107	23	10,658	23	NS
2nd quartile	11,750	1,139	23	10,611	23	
3rd quartile	11,751	1,112	23	10,639	23	
4th quartile	12,110	1,218	25	10,892	24	
Unknown	3144	302	6	2,842	6	
Urban-rural residence						
Metropolitan	42,941	4,098	84	38,843	85	.042
Nonmetropolitan	7,579	780	16	6,799	15	
Region						
Northeast	13,346	1,189	24	12,157	27	.0055
South	8,211	804	16	7,407	16	
Midwest	7,612	738	15	6,874	15	
West	21,351	2,147	44	19,204	42	
Married						
Yes	30,343	3,256	67	27,087	59	< .001
No	17,213	1,431	29	15,782	35	
Unknown	2,964	191	4	2,773	6	
Grade						
1	7,459	115	2	7,344	16	< .001
2	16,821	596	12	16,225	36	
3	12,566	1,971	40	10,595	23	
4	9,425	1,874	38	7,551	17	
Unknown	4,249	322	7	3,927	9	
AJCC stage						
0	15,187	379	8	14,808	32	< .001
I	26,581	1,691	35	24,890	55	
II	5,858	1,440	30	4,418	10	
III	2,894	1,368	28	1,526	3	
Lymph node involvement						
Negative	2,797	2,079	43	718	2	< .001
Unknown/not evaluated	47,723	2,799	57	44,924	98	
Chemotherapy						
Systemic ± intravesical	7368	949	19	6,419	14	< .001
Intravesical only	1,932	114	2	1,818	4	
None	41,220	3,815	78	37,405	82	
Charlson comorbidity score						
0	27,449	3,069	63	24,380	53	< .001
1	12,717	1,133	23	11,584	25	
≥ 2	10,354	676	14	9,678	21	
History of chronic kidney disease						
Yes	2,809	187	4	2,622	6	< .001
No	47,711	4,691	96	43,020	94	

(continued on following page)

Table 1. Characteristics of Cohort by Cystectomy Status (continued)

Characteristic	All Patients	Cystectomy No.	Cystectomy %	No Cystectomy No.	No Cystectomy %	*P*
History of fracture						
Yes	3,074	242	5	2,832	6	< .001
No	47,446	4636	95	42,810	94	
Urinary diversion						
Continent	721	721	15	N/A		
Incontinent	3,892	3,892	80	N/A		
Unknown	265	265	5	N/A		

NOTE. *P* value for unadjusted association between characteristics and receipt of cystectomy. History of chronic kidney disease on the basis of diagnosis codes from inpatient and outpatient claims in year prior to bladder cancer diagnosis. History of fracture on the basis of diagnosis codes from inpatient and outpatient claims in the year prior to bladder cancer diagnosis or cystectomy.
Abbreviations: AJCC, American Joint Committee on Cancer; N/A, not applicable; NS, not significant.

and phosphate balance.[7-11] Ileal resection may also compromise calcium absorption given that the majority of the ingested calcium is thought to be absorbed in the ileum.[12-14] It is plausible that the combination of these factors might cause osteoporosis and increase the risk of fractures.

However, whether urinary diversion with intestinal segments actually leads to increased risk of fractures has not been well established.[15] Prior studies have been limited because of small sample size, cross-sectional study design, limited duration of follow-up, lack of a control group, and use of intermediate outcomes such as serum and urinary electrolytes, bone resorption markers, and bone density rather than use of the occurrence of fractures as an end point. Hence, there is no consensus nor are there guidelines for screening or prophylaxis of osteoporosis for these patients. Our objective was to assess whether radical cystectomy and intestinal urinary diversion are associated with increased risk of fracture in a population-based cohort of patients with bladder cancer.

Table 2. Site of First Fracture by Receipt of Cystectomy

Fracture Site	Cystectomy (n = 792) No. of Patients	Cystectomy (n = 792) %	No Cystectomy (n = 10,080) No. of Patients	No Cystectomy (n = 10,080) %
Skull	50	6	570	6
Spine	224	28	2,635	26
Rib	109	14	1,436	14
Pelvis	42	5	509	5
Upper arm	73	9	822	8
Lower arm	43	5	622	6
Hand	30	4	581	6
Femoral neck	102	13	1,355	13
Other parts of femur	*	< 1	60	1
Lower leg	51	6	614	6
Foot	37	5	557	6
Pathologic fracture, unspecified	*	< 1	65	1
Other	23	3	254	3

NOTE. Cell counts < 11 masked in accordance with SEER-Medicare Data Use Agreement.

PATIENTS AND METHODS

Data Source

The primary data source was the National Cancer Institute's SEER-Medicare database, which links information from the SEER cancer registry program with Medicare claims and enrollment records. The SEER program is a consortium of cancer registries in selected states and geographic areas covering approximately 28% of the US population. For all incident cancers, the SEER registries collect information regarding site and extent of disease, clinical and pathologic stage, first course of cancer-directed therapy, and sociodemographic characteristics with active follow-up for date and cause of death.[16,17] Medicare is the primary health insurer for 97% of the US population age 65 years and older, covering inpatient hospital care (part A) and outpatient care and physician services (part B). Compared with the general US population age 65 years and older, the SEER-Medicare population has similar age and sex distributions but has a smaller proportion of nonwhites and a higher proportion of patients living in urban and affluent areas.[16,17] The SEER-Medicare files were used in accordance with a data-use agreement with the National Cancer Institute, and the study was reviewed and deemed exempt by the institutional review board at Memorial Sloan Kettering Cancer Center.

Study Cohort

We identified all cases of nonmetastatic bladder cancer diagnosed between 2000 and 2007. The cohort was restricted to patients age 66 years or older at diagnosis and a full year of Medicare claims before diagnosis for

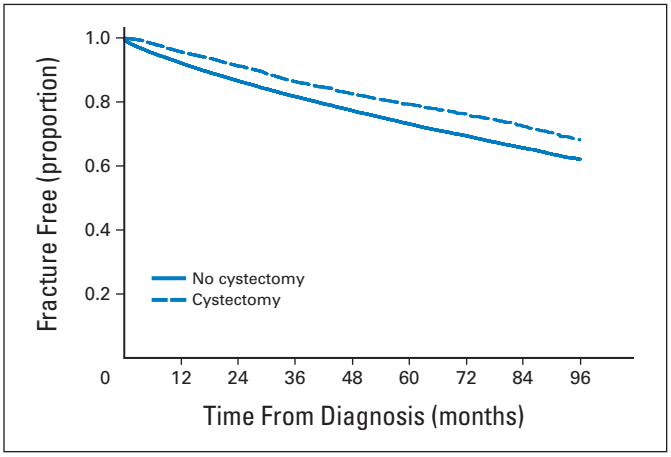

Fig 1. Fracture-free survival by receipt of cystectomy.

Table 3. Predictors of Time to First Fracture

Characteristic	Adjusted Hazard Ratio	95% CI	*P*
Cystectomy			
No	Reference		< .001
Yes	1.21	1.10 to 1.32	
Age at diagnosis, years			
66-69	Reference		< .001
70-74	1.22	1.13 to 1.31	
75-79	1.49	1.39 to 1.60	
≥ 80	2.17	2.02 to 2.32	
Sex			
Male	Reference		< .001
Female	1.61	1.54 to 1.68	
Race			
White	Reference		< .001
Black	0.48	0.42 to 0.55	
Hispanic	0.78	0.64 to 0.95	
Other	0.85	0.75 to 0.95	
Census tract median income			
1st quartile	Reference		NS
2nd quartile	0.99	0.93 to 1.05	
3rd quartile	1.00	0.94 to 1.06	
4th quartile	1.04	0.98 to 1.10	
Unknown	1.07	0.99 to 1.17	
Urban-rural residence			
Nonmetropolitan	Reference		NS
Metropolitan	1.06	0.99 to 1.12	
Region			
Midwest	Reference		< .001
South	1.13	1.05 to 1.21	
Northeast	0.99	0.93 to 1.06	
West	1.06	1.00 to 1.12	
Married			
Yes	Reference		< .001
No	1.13	1.08 to 1.18	
Unknown	0.98	0.90 to 1.06	
Grade			
1	Reference		NS
2	0.98	0.92 to 1.03	
3	1.02	0.95 to 1.08	
4	1.00	0.94 to 1.08	
Unknown	1.03	0.95 to 1.12	
AJCC stage			
0	Reference		< .001
I	1.05	0.99 to 1.11	
II	1.22	1.12 to 1.33	
III	1.29	1.15 to 1.46	
Lymph node involvement			
Negative	Reference		< .001
Unknown/not evaluated	1.38	1.23 to 1.54	
Chemotherapy			
None	Reference		< .001
Systemic ± intravesical	0.56	0.53 to 0.60	
Intravesical only	0.49	0.43 to 0.55	
Charlson comorbidity score			
0	Reference		< .001
1	1.23	1.18 to 1.29	
≥ 2	1.55	1.47 to 1.63	
History of chronic kidney disease			
No	Reference		< .001
Yes	1.16	1.06 to 1.26	
History of fracture			
No	Reference		< .001
Yes	2.97	2.80 to 3.15	
Year of diagnosis	1.00	0.98 to 1.01	NS

NOTE. History of chronic kidney disease on the basis of diagnosis codes from inpatient and outpatient claims in the year prior to bladder cancer diagnosis. History of fracture on the basis of diagnosis codes from inpatient and outpatient claims in the year prior to bladder cancer diagnosis or cystectomy.
Abbreviations: AJCC, American Joint Committee on Cancer; NS, not significant.

identifying comorbid conditions and prior fractures. We excluded patients with American Joint Committee on Cancer (AJCC) stage IV cancer (T4, lymph node involvement or metastases) or unknown stage of disease. Patients diagnosed at the time of death were excluded, as were patients who did not have complete Medicare coverage or were enrolled in a Medicare managed care plan at the time of diagnosis.

Outcomes

The primary end point was occurrence of a fracture at any site, identified in Medicare claims by the International Classification of Diseases, ninth revision (ICD-9) diagnosis codes for fracture or pathologic fracture (Appendix Table A1, online only).

Predictors

The predictor of interest was receipt of radical cystectomy with urinary diversion, identified in Medicare claims by ICD-9 procedure codes and Current Procedural Terminology codes any time after diagnosis. Diversion procedures were classified as continent, incontinent, or type unknown. Other bladder cancer treatments ascertained from Medicare claims included intravesical and systemic chemotherapy (Appendix Table A1).

Several patient and disease characteristics were assessed as possible confounders. Demographic characteristics included age at diagnosis, race, marital status, geographic location, and residence in a metropolitan versus nonmetropolitan county. In the absence of individual-level information, census tract median income was categorized in quartiles and used as a measure of socioeconomic status. Disease characteristics included AJCC stage, grade, and nodal involvement. Comorbidity was estimated using a modification of the Charlson comorbidity index on the basis of inpatient, outpatient, and physician claims in the year before bladder cancer diagnosis.[18,19] We similarly identified patients with a history of chronic kidney disease and prior fracture on the basis of Medicare claims in the year before bladder cancer diagnosis.

Statistical Analysis

Unadjusted associations between patient and disease characteristics and receipt of cystectomy were assessed using χ^2 tests. The impact of cystectomy and urinary diversion on the risk of fracture was evaluated in a time-to-event framework, in which the time origin was the date of bladder cancer diagnosis and patients who did not have a fracture were censored at the end of 2009 or sooner if they died, enrolled in a health maintenance organization or unenrolled from Medicare part A or B. We also censored patients who developed bone metastases or malignant bone neoplasms, on the basis of the presence of relevant ICD-9 diagnosis codes in Medicare claims (Appendix Table A1). Kaplan-Meier survival functions were estimated, stratified by treatment (cystectomy *v* no cystectomy) and type of urinary diversion (continent *v* incontinent). Multivariable Cox proportional hazards regression was used to estimate the impact of cystectomy on fracture risk, controlling for demographic, disease, and health characteristics. To examine the impact of cystectomy on subsequent rather than prior fractures, and because patients varied in the time between diagnosis and cystectomy, receipt of cystectomy was analyzed as a time-dependent variable, with exposure identified at the time of first Medicare claim for surgery. Adjusted hazard ratios (aHRs), 95% CIs, and two-sided

P values were estimated for each covariate. To assess the presence of effect modification, we examined terms for the interaction between cystectomy and age, sex, stage, and comorbidity. We also performed a separate analysis of the cystectomy group with known diversion type to estimate the impact of type of diversion on fracture. Statistical analyses were performed using SAS, version 9.2 (SAS Institute, Cary, NC).

RESULTS

The study cohort included 50,520 patients with nonmetastatic bladder cancer diagnosed between 2000 and 2007, of whom 4,878 (10%) had cystectomy and urinary diversion. Patients who had a cystectomy were younger, had fewer comorbidities, and were less likely to have a history of chronic kidney disease or fracture (Table 1). They also had more advanced AJCC stage and grade and were more likely to receive systemic chemotherapy. The groups were comparable with respect to sex and race and lived in areas with similar median income.

During a median follow-up of 41 months, 10,872 patients (22%) had a fracture, including 792 (16%) of those who had cystectomy and urinary diversion and 10,080 (22%) of those with no cystectomy. The median time to fracture was 16.6 months from cystectomy (interquartile range, 6.2-35.4 months) in the cystectomy group and 21.8 months from cancer diagnosis (interquartile range, 8.3-42.2 months) in the no cystectomy group. The incidence of fracture in the cystectomy group was 6.55 fractures per 100 person-years, compared with 6.39 fractures per 100 person-years in those without cystectomy. The type of fracture did not vary substantially between the two groups (Table 2).

In unadjusted analysis, fracture-free survival was better in patients who received cystectomy compared with those who did not (Fig 1). However, controlling for patient, disease, and health characteristics, radical cystectomy and urinary diversion increased the hazard of fracture by 21% (aHR, 1.21; 95% CI, 1.10 to 1.32; $P < .001$). The fracture hazard was also significantly greater among older patients, females, whites, those with more advanced disease, and those with a history of chronic kidney disease or fracture. Receipt of chemotherapy was associated with lower hazard of fracture (Table 3).

We found significant interactions between cystectomy and age and cystectomy and bladder cancer stage. Cystectomy had the greatest impact on fracture risk in the youngest patients (age, 66-69 years), with an aHR of 1.83 (95% CI, 1.47 to 2.29; $P < .001$; Table 4). Cystectomy also significantly increased the hazard of fracture in those age 75 to 79 years but not in other age groups. aHRs were fairly similar and statistically significant across stages of disease, except in patients with stage II bladder cancer. Interactions between cystectomy and sex and cystectomy and comorbidity were not statistically significant.

In patients who had a cystectomy with known urinary diversion type, in unadjusted analysis, the continent diversion group had better fracture-free survival than patients with incontinent diversion (Fig 2). However, in adjusted analysis there was no difference in fracture hazard by the type of diversion, controlling for demographic, disease, and health characteristics. Compared with patients who had continent diversion, those with incontinent diversion had a similar risk of fracture after radical cystectomy (aHR, 1.15; 95% CI, 0.93 to 1.43; $P = .21$).

Table 4. Adjusted Impact of Cystectomy on Time to First Fracture by Age and Stage

Stratum	Impact of Cystectomy		
	Adjusted Hazard Ratio*	95% CI	*P*
Age at diagnosis, years			
66-69	1.83	1.47 to 2.29	< .001
70-74	1.13	0.93 to 1.37	NS
75-79	1.29	1.08 to 1.53	.0043
≥ 80	0.97	0.82 to 1.15	NS
AJCC stage			
0	1.48	1.10 to 1.99	.0093
I	1.27	1.11 to 1.44	< .001
II	1.04	0.86 to 1.25	NS
III	1.39	1.09 to 1.77	.008

Abbreviations: AJCC, American Joint Committee on Cancer; NS, not significant.
*Hazard ratio for impact of cystectomy on fracture adjusted for all demographic, disease, and health characteristics in Table 3.

DISCUSSION

In this population-based cohort of older patients with bladder cancer, we found that radical cystectomy and urinary diversion were associated with an increased risk of fracture. Interestingly, patients who had cystectomy seemed to have fewer risk factors for fracture at the time of cancer diagnosis, given that they were generally younger, had fewer comorbidities, were less likely to have chronic kidney disease, and had a lower incidence of fractures in the year before diagnosis. Despite these favorable characteristics, after cystectomy their risk of fracture was increased by 21%, compared with their peers who did not have cystectomy.

These results have strong biologic plausibility, given that cystectomy and urinary diversion lead to chronic metabolic acidosis, which is associated with bone loss through bone resorption and urinary calcium loss. Prior studies that evaluated the association between urinary diversion and bone health were case series or cross-sectional studies with small sample sizes, poorly defined entry criteria, and poorly matched controls.[15] Moreover, none evaluated fracture as an

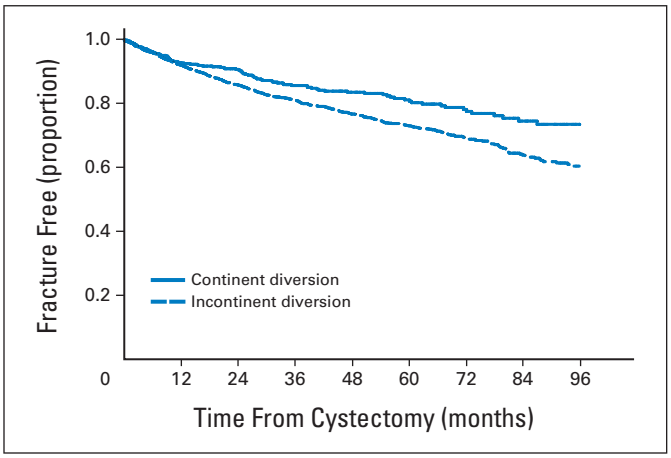

Fig 2. Fracture-free survival by type of urinary diversion in patients who received cystectomy.

end point, instead examining intermediate end points and finding conflicting results. Some studies showed decreased bone mineral density after cystectomy, and others did not.[15,20-30] Two longitudinal, prospective studies[31,32] found no decrease in bone density in the 2 or 3 years after cystectomy, but both had sample sizes of fewer than 50 patients. Similarly, there are conflicting results from studies of pediatric patients who have had augmentation cystoplasty or urinary diversion. Some of these studies reported decreased bone density and linear growth after augmentation cystoplasty or urinary diversion,[33-39] whereas others have not found such associations.[40-42]

In addition to bone loss, metabolic acidosis also increases protein catabolism and induces a negative nitrogen balance by increasing amino acid and protein degradation and decreasing albumin synthesis.[43-45] Treatment of acidosis has been shown to reverse these effects, decrease protein degradation, improve nitrogen balance, and increase serum albumin.[45-47] Therefore, it is plausible that the chronic metabolic acidosis after urinary diversion may lead to loss of muscle mass and strength, which may make these patients frail and more susceptible to falls and thus more likely to develop fractures.

Our findings have important implications for the management of patients with bladder cancer after radical cystectomy and urinary diversion. Currently, there are no guidelines for the detection and management of osteoporosis in these patients. Periodic monitoring of bone density and early initiation of treatment for osteoporosis may reduce the risk of fracture after cystectomy. Other strategies that may improve bone health and decrease fracture risk include prophylactic treatment of metabolic acidosis, oral supplementation of calcium and vitamin D3, and prophylactic treatment with oral bicarbonate.[11,48]

Our results may have broader implications for bone health beyond patients with intestinal urinary diversions. Endogenous acid production from dietary precursors has been hypothesized to lead to a state of chronic acidosis and cause age-related osteoporosis.[49] Diets rich in animal protein lead to a high acid load and cause metabolic acidosis even in healthy persons. High dietary acid load has been associated with increased bone resorption markers and decreased bone density in women and with lower bone cortical area and decreased bone mineral content in healthy children.[50-53] Although chronic metabolic acidosis is thought to lead to long-term bone loss, studies so far have not demonstrated an association between acidosis and increased risk of fractures. This may be the result of the lack of a large cohort of patients with chronic metabolic acidosis with long-term follow-up. Hence intestinal urinary diversion might be a suitable model to study the bone effects of chronic metabolic acidosis.

Patients who received chemotherapy appeared to have a lower risk of developing fractures. It is possible that this reflects selection bias if healthier patients were more likely to receive chemotherapy. Despite controlling for several patient characteristics, including comorbidity, there may have been residual confounding by other, unmeasured characteristics associated with overall health status and fracture risk. Other factors such as age, sex, race, comorbidities, chronic kidney disease, prior history of fracture, and region of the county were associated with fracture risk. These are all known risk factors for development of a fracture.[54-56]

Several limitations of our study should be noted. Although we controlled for numerous demographic, disease, and health characteristics, it is possible that the patients in our cohort who had cystectomy also had more aggressive cancers and hence were more susceptible to bone metastases and consequent pathologic fractures. To minimize confounding from bone metastases, we excluded patients with stage IV disease and with lymph node involvement, adjusted for disease stage and grade, and censored patients at the time of diagnosis of bone metastases or malignant bone neoplasm. We also found that cystectomy increased the risk of fracture across all cancer stages. Although we included pathologic fractures of unspecified site in the end point, these fractures constituted a very small proportion (1% or less) of all fractures among patients who had cystectomy and those who did not. Hence, our findings are unlikely to be explained primarily by pathologic fractures from bone metastases.

Other potential confounders that were not available in our data set included bone mineral density measures and use of medications for osteoporosis. Although these characteristics would likely be associated with fracture risk, it is not clear whether they would be differently distributed between the patients who received cystectomy and those who did not. Similarly, we had no information regarding patient preferences and physician recommendations for cystectomy.

We were also unable to identify metabolic acidosis as the cause of the increased risk of fractures for these patients. It is plausible that other factors associated with cystectomy such as frailty after major surgery may play a role. Finally, the results of our study, although generalizable to adults age 66 years and older, may not be applicable to younger patients with bladder cancer.

In summary, we found that radical cystectomy and urinary diversion were associated with an increased risk of fracture in older patients with bladder cancer. These findings emphasize the need to monitor bone health and to conduct trials of prophylactic therapies that may reduce the risk of fracture in these patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Amit Gupta, Behfar Ehdaie, Shahrokh F. Shariat, Farhang Rabbani, Harry W. Herr, Bernard H. Bochner, Elena B. Elkin
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Manuscript writing: All authors
Final approval of manuscript: All authors

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GLOSSARY TERMS

American Joint Committee on Cancer (AJCC)/ Union for International Cancer Control (UICC) TNM staging: a cancer staging system that describes the extent of cancer in a patient's body. "T" describes the size of the tumor and whether it has invaded nearby tissue; "N" describes regional lymph nodes that are involved; "M" describes distant metastasis (spread of cancer from one body part to another). The TNM Classification of Malignant Tumours was developed and maintained by the UICC to achieve consensus on one globally recognized standard for classifying the extent of spread of cancer. The TNM classification was also used by the AJCC. In 1987, the UICC and AJCC staging systems were unified into a single staging system. Prognosis of a patient is defined by TNM classification.

Cox proportional hazards regression model: a statistical model for regression analysis of censored survival data, examining the relationship of censored survival distribution to one or more covariates. This model produces a baseline survival curve, covariate coefficient estimates with their standard errors, risk ratios, 95% CIs, and significance levels.

osteoclast: a cell that breaks down bone and is responsible for bone resorption. Osteoclasts are large multinucleate cells that differentiate from macrophages.

Surveillance, Epidemiology, and End Results (SEER): a national cancer registry that collects information from all incident malignancies in multiple geographic areas of the United States.

Appendix

Table A1. Codes Used to Identify Diagnoses and Procedures

Diagnosis or Procedure	ICD-9	CPT/HCPCS
Radical cystectomy	57.7, 57.71, 57.79, 68.8	51570, 51575, 51580, 51585, 51590, 51595, 51596
Urinary diversion		
Continent	57.87	51596
Incontinent	56.51	50815, 50820, 51590, 51595
Chemotherapy		51720, 90586, 96400-96549, J0640, J8510, J8520, J8521, J8530, J8600, J8610, J8999, J9000-J9999, Q0083-Q0085
Intravesical therapy		51720, 90586, J9031
Fracture	733.1X (pathologic), 800-829	
Skull	800-804	
Spine	733.13, 805-806	
Rib	807	
Pelvis	808	
Upper arm	733.11, 810-812	
Lower arm	733.12, 813	
Hand	814-817	
Femoral neck	733.14, 820	
Other parts of femur	733.15, 821	
Lower leg	733.16, 822-824	
Foot	825-826	
Pathologic fracture, unspecified	733.1, 733.10	
Other	733.19, 809, 818-819, 827-829	
Bone metastases or bone neoplasm	198.5, 170.X	
Chronic kidney disease	585.X	

Abbreviations: CPT, current procedural terminology; HCPCS, Healthcare Common Procedure Coding System; ICD-9, International Classification of Diseases, ninth revision.