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Original Article

Trends in epidural anesthesia use at the time of radical cystectomy and its association with perioperative and survival outcomes: a population-based analysis

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Abstract: Epidural anesthesia is used to improve pain control after major surgeries. Few data describe the impact of epidural use for bladder cancer patients treated with radical cystectomy (RC). Here, we evaluate epidural use on perioperative and long-term outcomes for patients treated with radical cystectomy for bladder cancer. Patients who received radical cystectomy for non-metastatic bladder urothelial carcinoma with epidural (n=1,748) and without epidural (n=6,109) anesthesia from 2002-2014 were identified using Surveillance, Epidemiology and End Results-Medicare data. Radical cystectomy outcomes with and without epidural anesthesia were compared using propensity score weighting. Epidural use at time of radical cystectomy was identified in 1,748 (22.2%) of 7,857 patients who met inclusion criteria. After propensity score weighted adjustment, epidural use was associated with increased 30-day readmission (29.6% vs. 26.2%, P<0.001), increased median length of stay in days (9.0, IQR 7.0-12.0 vs 8.0, IQR 6.0-12.0, P<0.01), and decreased likelihood of being discharged directly to home without need for home health or skilled nursing care (21.6% vs 29.1%, P<0.001). Post-operative MI (2.6% vs 1.3%, P<0.001) in the first 30 days after radical cystectomy was more common in the epidural group, but perioperative 30-day mortality was similar (3.3% vs 2.9%, P=0.21). Epidural use was not associated with increased cancer specific (HR 0.96, 0.90-1.02, P=0.20) or overall survival (HR 0.99, 0.95-1.04, P=0.73). Epidural use at time of radical cystectomy is associated with increased risk of perioperative complications, hospital readmission, and longer hospitalization without improving disease specific survival. Prospective studies are needed to confirm these findings.

Keywords: Bladder cancer, epidural anesthesia, radical cystectomy

Introduction

Five-year bladder cancer-specific survival after radical cystectomy (RC) is stage-dependent, ranging from 33-64% [1]. Epidural use can reduce post-operative morbidity in open abdominal surgeries, which is important considering that over 60% of patients undergoing RC report complications within 90 days [2]. While minimally invasive approaches are becoming increasingly prevalent, over 80% of US cystectomies were open in 2012 [3]. Median hospital length of stay is greater than one week and readmission rate is 25-30% [3, 4]. Epidural use has been shown to improve these outcomes in non-urologic literature [5], though similar findings have not been described for RC. Enhanced recovery after surgery (ERAS) protocols have reduced length of stay, post-operative complications and readmissions but epidural use within these protocols are variable and not standardized [6].

Epidural use at time of abdominal surgery may also improve cancer outcomes by reducing the perioperative immunosuppressive effects of opioids and general anesthesia [7, 8]. Specifically, cancer recurrence and survival have been shown to be affected by application of regional anesthesia in observational studies, though not randomized trials [7, 9]. Single institution studies have suggested epidural use during transurethral resection of bladder tumor (TURBT) can reduce recurrence of non-invasive bladder cancer [10, 11]. There are limited studies available to evaluate the survival benefit of epidural use on bladder cancer after RC.

Epidural use at time of radical cystectomy is not included as a recommendation with high-grade

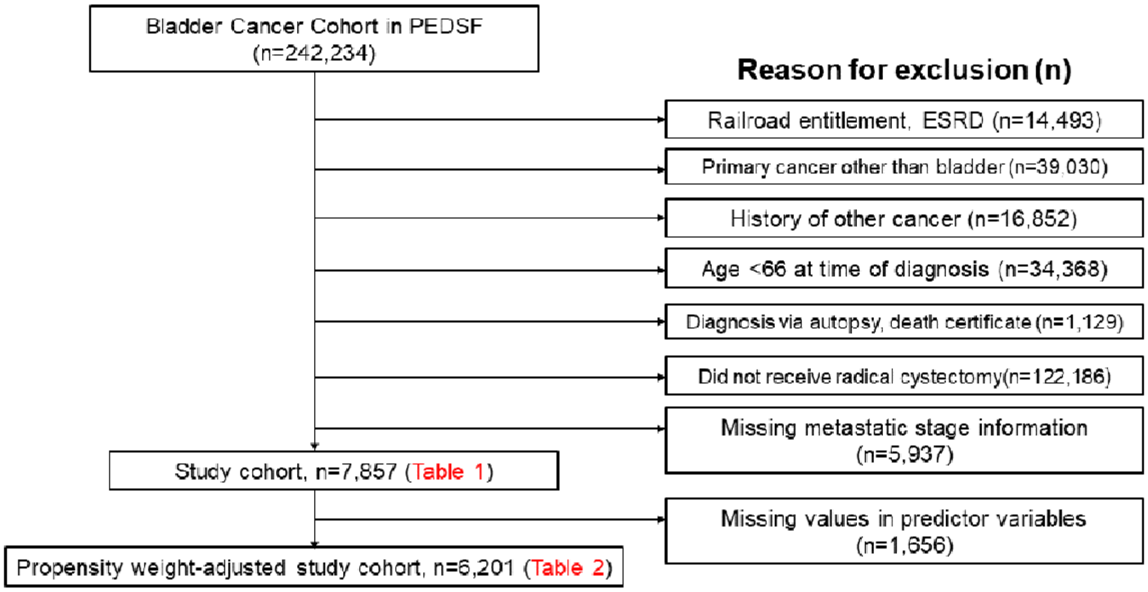

Figure 1. Study inclusion chart, SEER PEDSF database, 2002-2014. SEER = Surveillance, Epidemiology and End Results, PEDSF = Patient Entitlement and Diagnosis Summary File, ESRD = end stage rental disease.

levels of evidence in any of the current urologic guidelines given the lack of compelling data regarding reduction of post-operative morbidity or impact on cancer outcomes [12, 13]. The objective of our study was to analyze a large, contemporary population-based cohort to describe trends in epidural use, determine association of epidural use on bladder cancer specific survival after RC, and estimate morbidity and peri-operative outcomes associated with epidural use after RC.

Methods and materials

Data source

The Surveillance, Epidemiology and End Results (SEER) program and Medicare-linked data from 2002-2014 were acquired and analyzed. SEER collects cancer incidence and survival outcomes from population-based cancer registries in eight states and nine metropolitan, multi-county and rural areas covering approximately 28% of the US population [14].

Study population

Patients with urothelial cell carcinoma of the bladder were identified via the bladder cancer cohort of the Patient Entitlement and Diagnosis Summary File (PEDSF), which contains one record per person for individuals who have been matched with Medicare enrollment records, capturing 94% of persons in the SEER program data base diagnosed with cancer at age 65 or older [14]. Exclusion criteria were applied as follows (**Figure 1**): railroad entitlement/ESRD as reason for Medicare enrollment, primary cancer other than bladder, history of other cancer, age <66 at time of diagnosis, diagnosis via autopsy/death certificate, metastatic disease at diagnosis and those who did not receive radical cystectomy. RC was defined as International Classification of Disease, 9th revision (ICD-9) procedure code 57.71, 57.6, 57.7 or 57.79.

Exposure and study outcomes

Receipt of epidural anesthesia was defined according to the following Healthcare Common Procedure Coding System (HCPCS) codes within the National Claim History carrier file: 01996, 50171, 62310, 6682, 62311, 50837, 62318, 6819, 62319, 7327, 64450, 18488, 64999, as described in part previously [15]. Overall and cancer-specific survival were designated as the time from index surgery to the time of death. Censoring occurred if persons were alive at the end of the study period, December 31, 2014, or alternatively the date of their last claim per Medicare enrollment records. Overall survival was based on death from any cause while bladder cancer-specific survival was identified via PEDSF.

In-hospital and perioperative outcomes included readmission within 30 days after discharge from index hospitalization, length of stay and discharge disposition. Major events within 30 days were defined as death, myocardial infarction, pulmonary embolism and stroke. Other events of interest within 30 days were ileus, acute kidney injury, surgical site infection, sepsis, deep venous thrombosis, hypotension and clostridium difficile colitis.

Independent variables

Demographic characteristics included age, sex, race/ethnicity, marital status, SEER region and year of diagnosis. Census tract data from 2010 were used to estimate income, education and urban residence. Age-adjusted Charlson comorbidity index was generated as a composite variable based on diagnoses of individual comorbidities within the preceding 12 months [16].

Cancer-specific factors assessed were tumor stage and nodal stage. Since the 1973 World Health Organization (WHO) classification of NMIBC grading changed from G1-G3 to the current low-grade/high-grade system in 2004, grade was not utilized as this change fell within the study period and represented a potential source of misclassification bias.

Treatment factors were receipt of neoadjuvant chemotherapy and surgical approach. Identification of minimally invasive/robotic approaches has been described previously [3].

Statistical analysis

Demographic, tumor, comorbidity and treatment factors associated with epidural use were investigated with univariable logistic regression models. Factors with at least one level achieving statistical significance were included in a multivariable logistic regression model. Odds ratios, confidence intervals and *p*-values were generated at an alpha level of 0.05.

In-hospital, perioperative and survival outcomes were adjusted for potential confounding via propensity score adjustment. Propensity score adjustment is commonly used for population-based analysis as it can minimize confounding by pretreatment characteristics and mathematically achieve treatment groups which approach experimental design. This ensures that the effects observed are attributable to the treatment rather than inherently dissimilar factors between treatment groups [17]. Propensity scores were generated via multivariable logistic regression with demographic, tumor, comorbidity and treatment factors as input variables. Individuals weights were generated as (1/propensity score) for those who received epidural and the inverse of (1-propensity score) for those without epidural anesthesia. These weights were subsequently used in adjusted analyses. Persons with missing data in at least one of the predictor variables significantly associated with epidural use in univariable models (**Table 1**) were excluded from this propensity adjusted cohort (**Figure 1**).

In-hospital and perioperative outcomes were assessed via Chi-square tests in the unadjusted and stratified Mantel-Haenszel Chi-square in the adjusted models. Kaplan Meier survival curves for overall and cancer specific survival were constructed for the overall cohort and the propensity adjusted cohort. Cox proportional hazard models assessed bladder cancer-specific and overall survival in the propensity adjusted cohort.

All analyses were performed using SAS v9.4 (SAS Institute Inc., Cary, NC, USA).

Sensitivity analysis

After exclusion criteria were applied, there were 5,937 patients with RC but missing staging data which were excluded from the analytic cohort. To assess the potential of selection bias on survival, we performed a sensitivity analysis. Here, we considered the analytic cohort (**Figure 1**, n=7,857) of patients with complete staging data and those with missing staging data (n=5,937). To assess the possibility of disproportionate missing data by epidural use, we subsequently created three sets of Kaplan Meier curves, (1) pooled cohort (n=13,794, Supplementary Figure 1) stratified by presence or absence of available staging data, (2) pooled cohort stratified by use of epidural at time of RC (Supplementary Figure 2) and (3) those with absent staging data stratified by use of epidural at time of RC (Supplementary Figure 3). Adjusted and unadjusted models were created for each iteration.

Results

We identified 7,857 patients who had a RC for bladder cancer and met inclusion criteria.

Table 1. Univariate and multivariate analysis of epidural use at time of radical cystectomy by demographic, tumor and treatment-specific characteristics

	Frequency, n (%)		Univariate logistic regression analysis		Multivariate logistic regression analysis†	
	Epidural, n=1,748	No Epidural, n=6,109	Odds Ratio (95% CI)	*p*-value	Odds Ratio (95% CI)	*p*-value
Median age, yrs (IQR)	74.0 (70.0-78.0)	74.0 (70.0-79.0)	0.99 (0.98-1.01)	0.44		
Sex						
Female	345 (19.7)	1,153 (18.9)	Ref			
Male	1,403 (80.3)	4,956 (81.1)	0.95 (0.83-1.08)	0.42		
Race/Ethnicity						
White	1,615 (92.4)	5,443 (89.1)	Ref		Ref	
Black	46 (2.6)	291 (4.8)	0.53 (0.39-0.73)	0.01	0.55 (0.40-0.76)	0.01
Other	87 (4.9)	375 (6.1)	0.78 (0.62-0.99)	0.04	1.01 (0.79-1.30)	0.91
Marital Status						
Single	106 (6.3)	426 (7.3)	Ref			
Married	1,188 (71.0)	4,095 (69.9)	1.12 (0.93-1.46)	0.18		
Other	378 (22.6)	1,341 (22.9)	1.13 (0.89-1.44)	0.31		
Median income‡						
<Q1	542 (31.0)	1,920 (31.4)	Ref			
Q1-Q3	851 (48.7)	2,746 (45.0)	1.10 (0.97-1.24)	0.07		
>Q3	355 (20.3)	1,443 (23.6)	0.87 (0.75-1.01)	0.13		
Percent college educated§						
<Q1	541 (31.0)	1,932 (31.6)	Ref		Ref	
Q1-Q3	438 (25.1)	1,347 (22.1)	1.16 (1.01-1.34)	0.04	1.09 (0.94-1.28)	0.28
>Q3	769 (44.0)	2,829 (46.3)	0.97 (0.86-1.10)	0.64	1.08 (0.94-1.24)	0.25
Urban residence¶						
Metro	1,353 (77.4)	5,346 (87.5)	Ref		Ref	
Non-metro	395 (22.6)	763 (12.5)	2.05 (1.79-2.34)	<0.001	1.75 (1.50-2.04)	<0.001
Region						
Midwest	328 (18.8)	566 (9.3)	Ref		Ref	
Northeast	333 (19.1)	1,173 (19.2)	0.49 (0.41-0.59)	<0.001	0.58 (0.47-0.70)	<0.001
South	415 (23.7)	1,320 (21.6)	0.54 (0.46-0.65)	<0.001	0.55 (0.46-0.66)	<0.001
West	672 (38.4)	3,050 (49.9)	0.38 (0.32-0.45)	<0.001	0.45 (0.38-0.54)	<0.001
Year of diagnosis						
2008 or before	884 (50.6)	2,446 (40.0)	Ref		Ref	
2009 or after	864 (49.4)	3,663 (60.0)	0.65 (0.59-0.73)	<0.001	0.75 (0.67-0.84)	<0.001
Age-adjusted Charlson comorbidity index						
2	83 (4.8)	275 (5.7)	Ref			
3	303 (17.7)	817 (17.2)	1.23 (0.93-1.62)	0.15		
4	316 (18.5)	912 (19.1)	1.15 (0.87-1.51)	0.33		
5+	1,010 (59.0)	2,760 (57.9)	1.21 (0.94-1.57)	0.14		
Tumor stage						
<T2	584 (33.4)	2,179 (35.7)	Ref			
T2	579 (33.1)	1,995 (32.7)	1.08 (0.95-1.23)	0.23		
T3+	580 (33.2)	1,910 (31.3)	1.13 (1.00-1.29)	0.06		
Neoadjuvant chemotherapy						
No	837 (47.9)	3,871 (63.4)	Ref		Ref	
Yes	911 (52.1)	2,238 (36.6)	1.88 (1.69-2.10)	<0.001	1.89 (1.69-2.11)	<0.001
Surgical approach						
Robotic	66 (3.8)	802 (13.1)	Ref		Ref	
Open	1,682 (96.2)	5,307 (86.9)	3.85 (2.98-4.98)	<0.001	3.64 (2.79-4.75)	<0.001

IQR=interquartile range; Q=quartile; CI=comorbidity index; †Variables included in multivariate analysis were those with at least one statistically significant level according to univariate analysis; ‡Per reported household income for 2000 US census; §Per some college education as reported for the 2000 US census; ¶Based on metropolitan statistical area designations from the US census bureau.

Median age was 74.0 years (IQR 70.0-78.7). The cohort was predominantly male (80.9%) and of white ethnicity (89.8%). Epidural use at time of cystectomy was identified in 1,748 (22.2%) patients (**Table 1**). Epidural use declined with time, from 30.7% in 2005 to 14.8% in 2014 (P<0.001, data not shown).

Of 7,857 patients in the study cohort, 1,656 had missing data in key predictor variables and were excluded, leaving 6,201 in a propensity weight-adjusted study cohort. In a propensity score adjusted model, epidural use at time of RC was independently associated with increased 30-day readmission (29.6% vs. 26.2%, P< 0.001, **Table 2**), increased median length of stay in days (9.0, IQR 7.0-12.0 vs 8.0, IQR 6.0-12.0, P<0.01), and decreased likelihood of being discharged directly to home without need for home health or skilled nursing care (21.6% vs 29.1%, P<0.001) while adjusting for potential confounding variables. Those with epidurals were slightly more likely to suffer from post-operative MI (2.6% vs 1.3%, P<0.001) and stroke (4.7% vs 3.9%, P=0.028) in the first 30 days after RC, but no difference was observed for death (3.3% vs 2.9%, P=0.205). Similar post-operative results were found when excluding the small proportion of robotic RC patients, though notably stroke was not significantly associated with epidural use.

Cancer specific and overall survival after RC did not significantly differ by epidural use in unadjusted and adjusted KM curves (**Figure 2**). In a Cox proportional hazards model for survival with propensity score weight adjustment, epidural use was not associated with cancer specific (HR 0.96, 0.90-1.02, P=0.20) or overall survival (HR 0.99, 0.95-1.04, P=0.73, data not shown).

In a sensitivity analysis to estimate impact of excluding RC patients with absent stage data (n=5,937), cancer specific survival at 5 years was lower than that of the included study cohort (63.7% vs 67.3%, P<0.001, Supplementary Figure 1). Survival stratified by epidural use among a pooled cohort of those RC patients with and without absent staging data (n= 13,794) was similar in adjusted (67.7% vs 68.8%, P=0.55) and unadjusted (65.3% vs 67.1%, P=0.52) models (Supplementary Figure 2). Survival stratified by epidural use among the excluded RC patients only (n=5,937) was also similar in adjusted (67.7% vs 68.8%, P=0.77) and unadjusted (63.0% vs 66.8%, P=0.32) models (Supplementary Figure 3).

A separate sensitivity analysis was also conducted to elucidate any bias introduced by excluding those 1,656 with missing values in predictor variables (data not shown). Particularly, the measures at risk for bias are those in **Table 2**, including length of stay, re-admission, death within 30 days, and PE, stroke or MI within 30 days. When these measures were compared between the propensity weight-adjusted study cohort (6,201) and those excluded (1,656), only stroke was significantly different, occurring in 4.0% and 1.5% of the respective sample.

Discussion

In a large, population-based contemporary cohort undergoing RC for bladder cancer, epidural use was associated with increased rate of in-hospital complications, increased length of stay, use of ancillary services at discharge, and increased need for short term re-admission. Further, epidural use was not associated with improved cancer specific or overall survival. Collectively, these data suggest that epidural anesthesia may not be uniformly beneficial for patients treated with RC aside from post-operative narcotic-sparing analgesia. Although we also found that epidural use is decreasing, it is still a common adjunct to general anesthesia for RC patients in the United States.

Enhanced recovery after surgery protocols (ERAS) are multimodal care pathways aimed at reducing complications, expediting recovery and decreasing length of stay [6], and have been increasingly utilized in RC post-operative care. Protocols are not uniform and vary by institution and surgeon preference. Epidurals are not routinely incorporated in all protocols [18]. Epidural use within these pathways for RC has minimal evidence and not currently recommended by guidelines as a result [6, 12, 13].

In this context, our findings suggest that routine epidural use may not be beneficial to the goals of ERAS pathways. RC is associated with high post-operative morbidity with estimates greater than 60% in contemporary series [2]. Epidural use in open abdominal surgery has been shown to reduce select post-operative

Table 2. In-hospital and perioperative outcomes by epidural use at time of radical cystectomy before and after propensity score adjustment†

	Unadjusted analysis			Adjusted, robotic + open			Adjusted, open only		
	Epidural, n=1,748	No Epidural, n=6,109	*p*-value	Epidural, n=1,634	No Epidural, n=4,567	*p*-value	Epidural, n=1,571	No Epidural, n=3,974	*p*-value
Re-admission within 30 days	502 (28.7)	1,593 (26.1)	<0.001	479 (29.6)	1,203 (26.2)	<0.001	454 (28.7)	1,117 (25.3)	0.0031
Median length of stay, (IQR)	9.0 (7.0-13.0)	8.0 (6.0-12.0)	<0.001	9.0 (7.0-12.0)	8.0 (6.0-12.0)	0.0037	9.0 (7.0-13.0)	8.0 (6.0-12.0)	0.0021
Discharge disposition			<0.001			<0.001			<0.001
Home	405 (23.2)	1,812 (29.7)		376 (21.6)	1,313 (29.1)		368 (22.7)	1,184 (30.0)	
Home with health services	932 (53.3)	2,979 (48.8)		871 (54.7)	2,215 (48.4)		826 (52.7)	1,879 (47.4)	
Skilled nursing facility	361 (20.7)	1,185 (19.4)		343 (21.1)	931 (20.1)		333 (21.7)	813 (20.1)	
Death during index hospitalization	50 (2.9)	133 (2.1)		44 (2.5)	108 (2.4)		44 (2.8)	98 (2.5)	
Major event within 30 days									
Death	63 (3.6)	169 (2.8)	0.0681	57 (3.3)	129 (2.9)	0.2051	63 (3.7)	158 (3.0)	0.0653
Myocardial infarction	43 (2.5)	81 (1.3)	0.010	40 (2.6)	61 (1.3)	<0.001	40 (2.3)	75 (1.4)	0.0008
Pulmonary embolus	33 (1.9)	124 (2.0)	0.712	32 (1.9)	100 (2.2)	0.2990	32 (4.3)	107 (4.0)	0.5525
Stroke	72 (4.1)	199 (3.3)	0.081	66 (4.7)	180 (3.9)	0.0280	68 (2.0)	181 (2.1)	0.5460
Any of above	141 (8.1)	389 (6.4)	0.013	132 (8.9)	328 (7.1)	0.0004	189 (11.4)	487 (9.9)	0.0127
Other events within 30 days									
Ileus	596 (34.1)	1700 (27.8)	<0.001	552 (34.3)	1,298 (28.5)	<0.001	569 (33.9)	1,481 (28.6)	<0.001
Acute kidney injury	337 (19.3)	1,069 (17.5)	0.09	318 (19.9)	822 (17.8)	0.0021	322 (19.5)	885 (16.9)	0.0051
Surgical site infection	181 (10.4)	477 (7.8)	<0.001	168 (9.8)	380 (8.3)	0.0051	176 (10.2)	416 (8.2)	0.0015
Sepsis	356 (20.4)	1,001 (16.4)	<0.001	325 (20.1)	799 (17.4)	0.0001	345 (20.3)	859 (17.2)	<0.001
Deep venous thrombosis	130 (7.4)	360 (5.9)	0.02	121 (8.4)	307 (6.8)	0.0007	122 (7.7)	317 (6.8)	0.0632
Hypotension	334 (19.1)	656 (10.4)	<0.001	312 (18.7)	524 (11.5)	<0.001	319 (18.7)	543 (11.2)	<0.001
Clostridium difficile colitis	72 (4.2)	215 (3.5)	0.19	68 (4.5)	161 (3.5)	0.0052	68 (4.2)	178 (3.3)	0.0149

IQR=interquartile range; †Calculated based on designation of following demographic variables: age, sex, race, education, income, urban residence, date of diagnosis, tumor stage, nodal stage, receipt of neoadjuvant chemotherapy, surgical approach, age-adjusted Charlson comorbidity index.

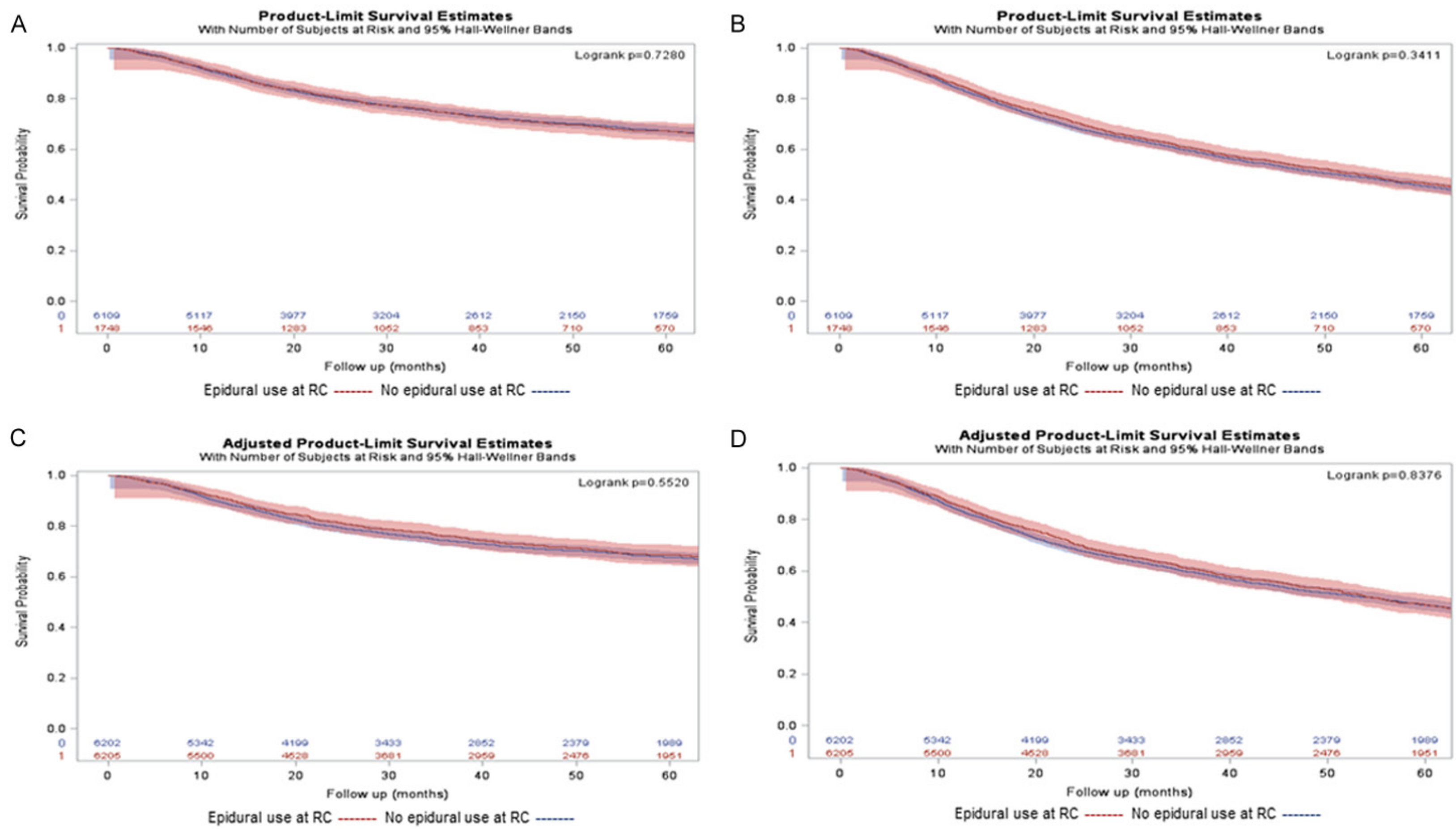

Figure 2. Kaplan Meier survival by epidural use. A. Cancer-specific survival, unadjusted. B. Overall survival, unadjusted. C. Cancer-specific survival with propensity-score adjustment. D. Overall survival with propensity-score adjustment.

morbidity outcomes in a large meta-analysis [5], though a separate meta-analysis focused on epidural use compared with patient controlled anesthesia as part of ERAS protocols and specifically showed increased morbidity [19]. We found that epidural use was actually associated with increased rates of ileus, though it is difficult to solely credit epidural use for this association without knowing other key components of care not obtainable with SEER data (e.g., opioid use, fluids, alvimopan use). We also found that epidural use was associated with increased odds of major 30-day complications, including myocardial infarction in our analysis that controlled for potential confounding variables. A post hoc analysis of 8,351 non-cardiac surgery patients at high cardiovascular risk undergoing non-urologic surgery suggested a similar association and showed the odds of post-operative MI associated with epidural vs GA in adjusted analysis was 3.2 (2.1-4.8) [20]. This association could be due to transient arterial hypotension known to be associated with epidural use which can lead to relative ischemia in patients with underlying atherosclerosis, potentially leading to post-operative MI. Bladder cancer patients have high rates of associated cardiovascular comorbidities [21]. Conversely, a single institution study found that there was no association between epidural use and post-operative RC complication rate [22]. The lack of literature consensus regarding morbidity and epidural use in open abdominal surgery generally and radical cystectomy specifically may be due to the heterogeneity of patient populations associated with different cancer types studied, differences in level and duration of spinal anesthesia, and heterogeneity of concomitant post-operative management (e.g., use of alvimopan, ERAS protocols).

Readmission rate is a quality and cost containment metric utilized by hospital administrators, policy makers, and payers. The Centers for Medicare and Medicaid's Hospital Readmission Reduction Program financially penalizes hospitals with high rates of Medicare readmissions [23]. Despite efforts like these, hospital readmission rate after cystectomy has been stable near 25% over the past decade, and Skolarus et al found that about 50% of readmissions from radical cystectomy last >5 days and are associated with significant cost [4]. Both post-operative length of stay and complications can be predictive of readmission [24]. Here, we describe a readmission rate of 29.6% associated with epidural use vs. 26.2% with general anesthesia only. Greater length of stay and need for ancillary services at discharge were also associated with epidural use. Contrasting with our results, a Canadian population-base study found that epidural use was not associated with increased length of stay or short or long-term readmission [25]. However, one important difference between was that the Canadian cohort was much younger (39% were <70 years of age), healthier (87% had CCI morbidity index of ≤1) and were more likely to receive epidural (54%). Therefore, it may be that older, comorbid patients are at a slight increased risk of readmission as noted in the elderly patients that received an epidural in our study.

In adjusted analyses, we found that epidural use was not associated with any oncologic outcomes as we had hypothesized a priori. Regional anesthesia has been shown to reduce cancer recurrence, progression, and mortality in multiple studies, potentially by surgical stress and opioid reduction, thereby indirectly blunting transient peri-operative immunosuppressive and angiogenic states [7]. In the bladder cancer literature specifically, the data is limited and generally restricted to single institution studies [26]. There may be a benefit for spinal anesthesia only on recurrence of non-muscle invasive bladder cancer at time of TURBT [10, 11]. Several important distinctions between these studies and ours should be recognized. First, we included patients who underwent RC and therefore included a larger percentage of higher risk patients. Second, the above studies which have shown benefit in cancer outcomes investigated epidural use only without concomitant general anesthesia, which is generally not applicable to patients undergoing RC. Therefore, the impact of epidural use on bladder cancer outcomes is likely not uniform but heterogenous across tumor characteristics, patient factors and other anesthetic considerations.

Our findings should be interpreted in the context of several study limitations. First, outcomes from SEER Medicare data are generated based on billing codes. Pertinent to this study, the data does not contain information on surgical margin positivity, cancer recurrence, or specifics and duration of epidural use and post-operative care. This includes but is not limited to quantitative measurements of peri-operative fluid and opioid use, intra-operative surgical factors, or reasons for re-admission. Though data granularity necessary to assess Clavien grade of complications is not available, validation studies have determined good accuracy of tracking inpatient complications (vs post-discharge complications) which were described here [27]. Further, the complication rates we report are similar to other studies [3, 28]. Second, the large number of patients excluded for missing staging information could be a potential source of selection bias. In fact, there was evidence of slightly reduced survival in those without complete staging information in our sensitivity analysis. Therefore, we likely overestimated survival overall. Importantly however, our sensitivity analysis also demonstrated no change in the association between epidural use and survival outcomes when stratifying by epidural use. We also conducted a sensitivity analysis to elucidate potential bias introduced by excluding those with missing predictor variables to generate the propensity weight-adjusted study cohort shown in **Table 2**, and did find a differential association with respect to stroke, though not other variables. Third, as this is a retrospective study it is subject to confounding factors. Propensity score analysis is robust analytic process to adjust for confounding in large population-based retrospective cohorts, though confounding can persist if unmeasured covariates are not accounted for [17]. Lastly, our findings may have limited generalizability to younger patients.

Conclusion

In a large, population-based contemporary cohort undergoing RC for bladder cancer, we found that epidural use was not associated with improved survival but is associated with increased rates of readmission, longer length of stay and increased in-hospital complication rates. Epidural use has also been declining in the United States. These results underscore the need for prospective, hypothesis-testing studies. While there are currently RCTs examining the association of peri operative epidural use and survival outcomes in breast, melanoma, lung and colon cancer, none are ongoing for bladder cancer [7]. Regardless, our results may inform current clinical bladder cancer guidelines, which generally lack evidence for epidural use, especially in era of prioritizing readmission reduction, improved quality and cost-containment.

Disclosure of conflict of interest

None.

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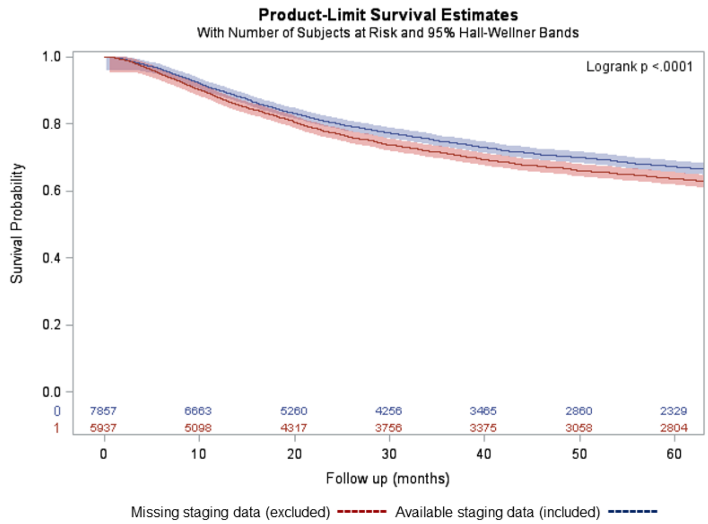
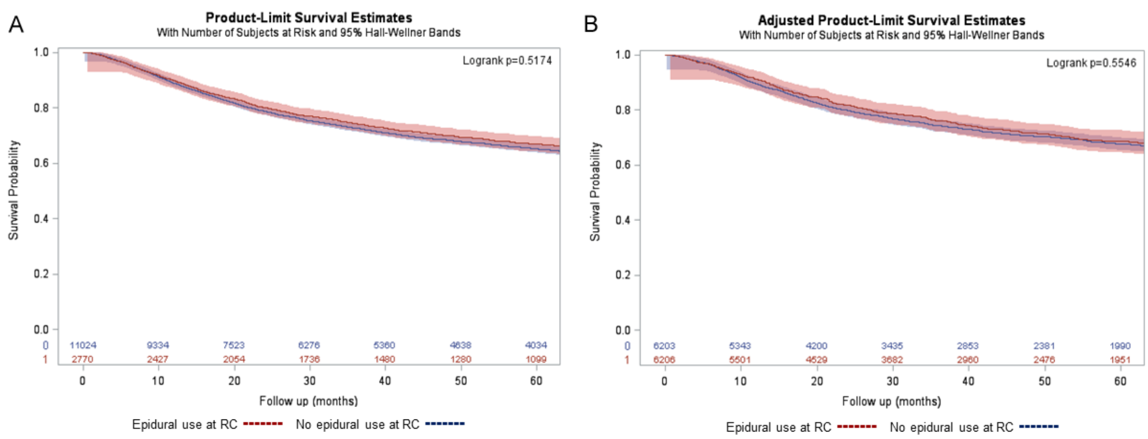
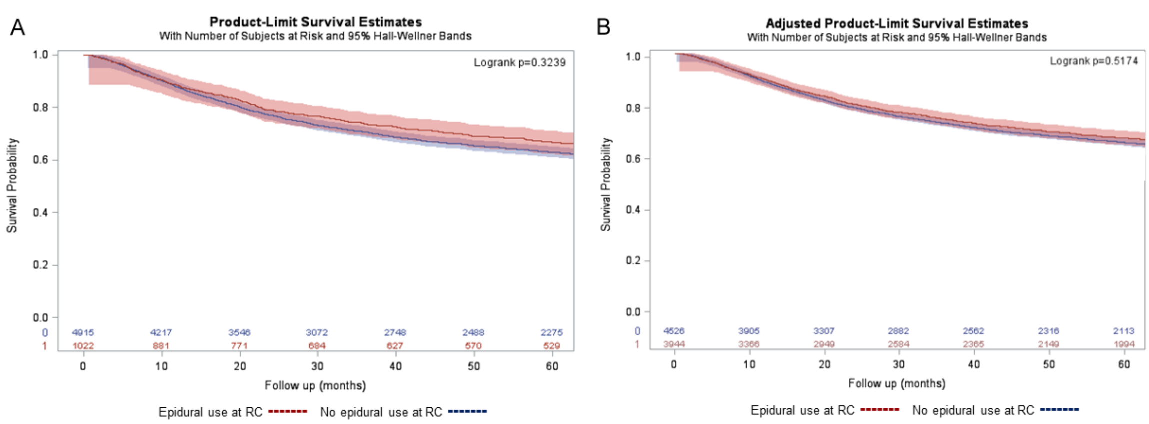


Supplementary Figure 1. Bladder cancer specific survival by included (n=7,857) and excluded (5,937) subjects based on missing staging data.



Supplementary Figure 2. Cancer-specific survival among pooled cohort (n=13,794) of included (n=7,857) and excluded (5,937) subjects based on missing staging data, by receipt of epidural anesthesia at time of RC. (A) Unadjusted, (B) Adjusted with propensity score weighting.



Supplementary Figure 3. Cancer-specific survival among excluded (5,937) subjects on missing staging data, by receipt of epidural anesthesia at time of RC. (A) Unadjusted, (B) Adjusted with propensity score weighting.