Burden and timing of venothrombolic events in patients younger than 65 years undergoing radical cystectomy for bladder cancer

Andrew C. James, M.D.*, Sarah K. Holt, Ph.D., Jonathan L. Wright, M.D., M.S., Michael P. Porter, M.D., M.S., John L. Gore, M.D., M.S.

Department of Urology, University of Washington School of Medicine, Seattle, WA

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Abstract

Introduction and objectives: Venothrombolic events (VTEs) following radical cystectomy (RC) are a significant contributor to postoperative morbidity. A better understanding of the incidence and timing of VTE would clarify chemoprophylaxis strategies among RC patients. We sought to characterize the burden of VTE after RC by defining their timing and effect utilizing the MarketScan commercial databases.

Methods: From MarketScan databases, we identified patients younger than 65 years undergoing RC for a primary diagnosis of bladder cancer between 2008 and 2011 with International Classification of Diseases, 9th Edition diagnosis and procedure codes. MarketScan includes inpatient and outpatient health insurance claims of 34 million enrollees annually with data from 150 employers and 13 commercial health plans. We identified the occurrence of VTE, including both pulmonary embolism and deep vein thrombosis, in patients undergoing RC by searching MarketScan for relevant International Classification of Diseases, 9th Edition codes for these diagnoses. Our primary outcome of interest was the timing of VTEs. Multivariate logistical regression models were used to identify patient factors that were associated with VTEs.

Results: A total of 1,581 patients were included in our analysis. Overall, 10% of patients experienced VTEs within 90 days of RC. The incidence of postoperative VTEs during the index admission, after discharge and within 30 days of surgery, and between 31 and 90 days postoperatively was 2.9%, 3.8%, and 3.3%, respectively. Prolonged index hospitalization, discharge to a skilled nursing facility, and orthotopic neobladder urinary diversion were significantly associated with VTE within 30 days of RC.

Conclusion: Most VTEs occur after discharge from the index RC hospitalization. Consideration should be given to extended chemoprophylaxis in this high-risk group of patients. © 2014 Elsevier Inc. All rights reserved.

Keywords: Bladder cancer; Radical cystectomy; Venothrombolic events; Chemoprophylaxis; Complications

1. Introduction

Venothrombolic events (VTEs) following radical cystectomy (RC) for treatment of bladder cancer are a significant contributor to postoperative morbidity. The incidence of VTE, including both pulmonary embolism and deep vein thrombosis, following RC has been reported as being 2% to 14% [1–4]. Patients undergoing RC have over a 3-fold higher risk for developing VTEs than patients undergoing other urologic oncology operations, such as nephrectomy and radical prostatectomy [4].

Patients with bladder cancer who undergo RC typically have many risk factors for VTEs including malignancy, increasing age, smoking history, and pelvic surgery [5]. Although guidelines offer recommendations for these high-risk patients in the immediate postoperative period, the optimal duration of chemoprophylaxis agents such as subcutaneous heparin and low-molecular-weight heparin in this patient population has not been clarified. Previous studies have shown that up to 80% of VTEs after radical prostatectomy occur following discharge from the index hospitalization [6]. This corroborates findings that a
substantial number of VTEs occur following discharge from the index hospitalization for resections for colorectal, gynecologic, breast, and hepatopancreaticobiliary malignancies [6,7]. Illustrating the potential benefit of extended chemoprophylaxis in high-risk patients, a randomized controlled trial of VTE prophylaxis after surgery for abdominal and pelvic malignancies demonstrated a reduction in the incidence of VTE from 12.0% to 4.8% among patients receiving extended chemoprophylaxis for 28 days compared with those receiving only 7 days of chemoprophylaxis [8].

These studies suggest a high risk of postoperative VTE after discharge. A better understanding of the incidence, timing, and setting of management of VTE would clarify chemoprophylaxis strategies following RC and could be associated with decreased morbidity and burden of readmissions. We sought to characterize the burden of VTE among patients younger than 65 years who underwent RC for bladder cancer utilizing a national commercial claims database.

2. Methods

We identified patients undergoing RC for a primary diagnosis of bladder cancer from MarketScan databases between 2008 and 2011. MarketScan comprises the inpatient and outpatient health insurance claims of more than 34 million enrollees annually from 150 employers and 13 commercial health plans across the United States. Patients 65 years of age and older may have dual coverage with Medicare with claims data not captured by MarketScan; thus, we restricted our analysis to enrollees younger than 65 years. Patients undergoing RC for a primary diagnosis of bladder cancer were identified by a combination of Common Procedural Terminology and International Classification of Diseases, 9th Edition (ICD-9) procedure and diagnosis codes (Appendix).

Incident postoperative VTEs, including deep vein thrombosis and pulmonary embolus, were identified by ICD-9 codes applying Agency for Healthcare Research and Quality Patient Safety Indicator software for Patient Safety Indicator 12. Those without a diagnosis of VTE in their claims for the 6-month period preceding RC who subsequently had a code for VTE during the index admission were considered to have developed the VTE during the index hospitalization. Patients without a history of VTE or a diagnosis of VTE during the index admission who subsequently had a code for VTE following discharge from the index admission were considered to have developed the VTE after discharge. VTE timing was recorded as occurring during the index hospitalization when RC was performed, after discharge but within 30 days of RC, and after discharge but within 90 days of RC based upon the corresponding date of diagnosis.

Multivariate logistical regression models were used to identify patient factors that were associated with VTEs after RC. Available patient demographic information included age, race/ethnicity, and gender. The clinical covariates that we evaluated included length of stay (LOS), burden of comorbidity conditions, type of urinary diversion (i.e., continent cutaneous or orthotopic neobladder vs. incontinent ileal conduit), receipt of neoadjuvant chemotherapy (NC), and discharge disposition. The association of VTE with other codiagnoses occurring during the index hospitalization (pneumonia, pyelonephritis, urinary tract infection, surgical site infection, and Clostridium difficile colitis) was also assessed by capturing ICD-9 codes occurring during the index hospitalization. Receipt of NC was captured by utilizing the billing codes for injectable therapies (J-codes) for doxorubicin, methotrexate, vinblastine, carboplatin, and gemcitabine; patients with a code for 1 or more of these chemotherapeutic agents listed within 6 months before RC were considered to have received NC. Comorbidity indices were calculated using the Klabunde modification of the Charlson comorbidity index [9]. To ensure ascertainment of patient comorbidities and adequate follow-up of postoperative VTE, we excluded patients who were not enrolled in MarketScan for 12 months before RC and 3 months post-RC (n = 524). We further excluded patients with a VTE in the 6 months preceding RC (n = 59). This study qualified for a waiver of institutional review board approval as the data are fully Health Insurance Portability and Accountability Act (HIPAA) compliant and completely deidentified.

3. Results

Of the 4,277 patients in MarketScan undergoing RC for a primary diagnosis of bladder cancer, 1,581 met our inclusion criteria and were included in our analysis. Overall, 44.5% of the cohort was 60 to 64 years of age and 78% were men. Of the patients, 95% were discharged home and 5% discharged to a skilled nursing facility. An ileal conduit urinary diversion was performed in 55% of patients and a neobladder in 37%; diversion type was unknown in 9% of patients. The index admission was 7 days or less in 48% of patients. NC was received by 14% of patients. Details of our patient cohort can be found in Table 1.

The incidence of postoperative VTEs during the index admission, after discharge and within 30 days of surgery, and between 31 and 90 days postoperatively was 2.9%, 3.8%, and 3.3%, respectively. Overall, 10% of patients experienced VTEs within 90 days of RC. The timing of VTE diagnosis influenced the management of these events. Of the VTEs that occurred after discharge but within 30 days of RC, 31% were managed in the outpatient setting, whereas 45% of the VTEs that occurred between 30 and 90 days postoperatively were managed in the outpatient setting. The all-cause readmission rate within 90 days of RC was 34%. Of those readmitted, 69% were readmitted once, 22% were readmitted twice, and 9% were readmitted 3 or more times. The median LOS for the first readmission was 4 days, and the average time to the first readmission was 33 (±21.8) days. For those without a VTE, there was a
In our study using MarketScan databases, we were able to quantify the timing of diagnosis of VTE after RC in patients younger than 65 years and examine the management setting associated with these events. Our study significant (odds ratio = 1.57, 95% CI: 0.99–2.50). VTEs that occurred between 31 and 90 days after RC did not demonstrate an association with LOS after RC, discharge disposition, NC, or urinary diversion type (data not shown). Although pneumonia, urinary tract infection, surgical site infections, Clostridium difficile colitis, and pyelonephritis were associated with longer LOS, they were not significantly associated with VTE, and the addition of these covariates had no effect on the risk estimates in the adjusted multivariate regression models (data not shown).

### 4. Discussion

In our study using MarketScan databases, we were able to quantify the timing of diagnosis of VTE after RC in patients younger than 65 years and examine the management setting associated with these events. Our study

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**Table 1**

Characteristics of study sample

<table>
<thead>
<tr>
<th>Total patient population (n = 1,581)</th>
<th>n</th>
<th>Percentage</th>
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| Age  
  <55  | 422 | 26.69  
  55–59 | 455 | 28.78  
  60–64 | 704 | 44.53  |
| Gender  
  Male | 1,234 | 78.05  
  Female | 347 | 21.95 |
| Charlson comorbidity index  
  0 | 1,080 | 68.31  
  1 | 325 | 20.56  
  ≥2 | 176 | 11.13  |
| Length of stay, d  
  ≤7 | 760 | 48.07  
  8–11 | 535 | 33.84  
  ≥12 | 286 | 18.09  |
| Discharge status  
  Home | 1,504 | 95.13  
  Skilled nursing facility | 77 | 4.87 |
| Diversion type  
  Ileal conduit | 867 | 54.84  
  Neobladder | 577 | 36.84  
  Unknown | 137 | 8.67  |
| Neoadjuvant chemotherapya  
  Yes | 216 | 13.66  
  No | 1,365 | 86.34 |

**Table 2**

Multivariate logistical regression analysis of factors associated with VTE within 30 d of RC

| Events Incidence Unadjusted OR Adjusted ORb | Age  
  ≤55 | 28 | 6.6 | Ref | Ref |
<table>
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<td>&lt;55–59</td>
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</tr>
<tr>
<td>60–64</td>
<td>47</td>
</tr>
</tbody>
</table>
| Gender  
  Male | 86 | 7 | Ref | Ref |
| Female | 18 | 5.2 | 0.73 (0.43–1.23) | 0.71 (0.42–1.22) |
| Charlson comorbidity index  
  0 | 79 | 7.4 | Ref | Ref |
| 1 | 15 | 4.7 | 0.61 (0.35–1.08) | 0.63 (0.35–1.13) |
| ≥2 | 10 | 5.7 | 0.76 (0.39–1.5) | 0.62 (0.3–1.27) |
| Length of stay, d  
  ≤7 | 31 | 4.1 | Ref | Ref |
| 7–11 | 38 | 7.1 | 1.8 (1.1–2.93) | 1.79 (1.09–2.93) |
| 12+ | 35 | 12.2 | 3.28 (1.98–5.43) | 3.13 (1.85–5.3) |
| Discharge status  
  Home | 92 | 6.2 | Ref | Ref |
| Skilled nursing facility | 11 | 14.3 | 2.56 (1.31–5.01) | 2.05 (1.02–4.14) |
| Died of PE | 1 | 100 | – | – |
| Diversion type  
  Ileal conduit | 43 | 5 | Ref | Ref |
| Neobladder | 48 | 8.3 | 1.74 (1.14–2.66) | 1.67 (1.07–2.60) |
| Unknown | 13 | 9.5 | – | – |
| Neoadjuvant chemotherapyb  
  No | 95 | 7.1 | Ref | Ref |
| Yes | 9 | 3.6 | 1.54 (0.98–2.52) | 1.57 (0.99–2.50) |

*Defined as receipt of doxorubicin, methotrexate, vinblastine, cisplatin, carboplatin, or gemcitabine within 6 mo of RC.

*Model included all variables.

OR = odds ratio; PE = pulmonary embolism.

Bold values indicate statistical significance.
indicates that most VTEs are diagnosed after discharge from the index admission. In addition, we were able to identify factors associated with an increased risk of VTE that may further warrant extended chemoprophylaxis. Increased utilization of chemoprophylaxis in these patient populations may reduce the occurrence of VTEs after RC.

Previous studies have examined the incidence of VTEs and have found that a significant proportion of these events occur after discharge from the index hospitalization. Agnelli et al. [10] found that VTEs were the most common cause of death within 30 days of cancer surgery, highlighting the significant burden of VTEs occurring postdischarge. Other investigators found that approximately 35% of patients developed a symptomatic VTE and required readmission following discharge from the index admission after RC [11]. The authors were only able to capture VTEs that necessitated readmission. Based on our data that a considerable number of VTEs are managed on an outpatient basis, these results likely underestimate the true incidence of postdischarge VTEs following RC. Risk factors that render patients undergoing RC high risk for VTE postdischarge include advanced age, malignancy, prevalent histories of tobacco use, pelvic surgery, and immobility associated with surgery [5]. We demonstrated that most of these events are diagnosed after discharge from the index hospitalization; the incidence of VTEs during the index hospitalization was 2.9% compared with 7.1% after discharge but within 90 days of RC.

Our analysis of timing of VTEs with respect to the management setting showed that more VTEs occurring early after discharge required inpatient management compared with VTEs occurring later in patients’ convalescence from RC. This may reflect the higher acuity of VTEs early after surgery or the higher acuity of the patient early after surgery. Providers likely have a lower threshold for readmission in the early postoperative period. We also showed that VTE contributes substantially to the overall burden of RC by being associated with an increased number of readmissions, including multiple readmissions.

Patient factors associated with an increased risk of VTE included continent urinary diversion and discharge to a skilled nursing facility. The association with neobladder reconstruction is interesting given that patients undergoing urinary diversion with a cutaneous or orthotopic neobladder typically are younger, healthier, and have better functional status than those undergoing ileal conduit urinary diversion [12]. Higher VTE rates may relate to the longer operative time required for the more complex neobladder reconstruction. Previous studies have shown that increased operative times are associated with higher risk for VTEs [6,13]. Also, patients undergoing orthotopic neobladder urinary diversion are often discharged with additional drains such as urethral catheters that may limit mobility, further increasing the risk of VTE during the postoperative period. Patients discharged to a skilled nursing facility may have compromised functional status that increases their risk for thrombotic events. Importantly, these facilities would be ideal locations for the safe administration of chemoprophylaxis and for monitoring for potential adverse events. Interestingly, we did not find an association between comorbidity and VTEs. It may be that RC is associated with significant burden irrespective of health status. Additionally, most of these patients still have multiple risk factors for VTEs irrespective of comorbidity.

Current guidelines support the use of perioperative chemoprophylaxis for RC care. The American Urological Association recommends use of both pneumatic compression devices and chemoprophylaxis among patients considered high risk for VTEs; most patients undergoing RC would be in this category owing to multiple risk factors [14]. These recommendations are for inpatient care, yet—despite these recommendations—there is still low self-reported compliance with these recommendations [15]. This may relate to the dearth of studies that have examined the potential role of chemoprophylaxis in RC care and provider concerns for hemorrhage. Although the 2012 Chest guidelines recommend extending chemoprophylaxis to 28 days postoperatively to reduce the risk of VTE, there is a severe paucity of data examining the utility of chemoprophylaxis after discharge from the index RC admission, and these recommendations are based on studies described as low to moderate quality and that do not specifically examine RC patients [16].

There are several limitations to our analysis. First, this is a retrospective review of a commercial claims database. Data are thus dependent upon accurate diagnosis and procedure coding and was not obtained through detailed analysis of patients’ clinical records. Second, not all relevant clinical data could be obtained from MarketScan. We did not have detailed information on drugs during inpatient or outpatient visits and could not identify use of VTE chemoprophylaxis. Based on our results, it will be important to clarify the comparative effectiveness of different chemoprophylaxis strategies after RC to determine whether VTE chemoprophylaxis reduces the high rates of postdischarge VTE that we identified. Third, our results may not be generalizable to the broader RC population. Our analysis included patients younger than 65 years with employer-provided health insurance. Although MarketScan does contain data for patients 65 years and older, dual coverage with Medicare limits complete ascertainment of billing claims. Despite this limitation, restricting our analysis to a younger, more functional population highlights that VTEs are a substantial burden even amongst younger RC patients. Our work provides preliminary evidence of the burden of VTEs beyond the index admission and illustrates the need for further studies to better define the potential benefit of routine extended chemoprophylaxis.

5. Conclusion

Patients undergoing RC for bladder cancer are at high risk for VTEs. Most of these events occur after discharge from the index RC hospitalization. Although future studies must clarify the optimal duration and potential risks associated with
extended chemoprophylaxis, consideration should be given to extended chemoprophylaxis in this high-risk group of patients.

Appendix

**Codes for identification of RC**

Common Procedural Terminology: 51570, 51575, 51590, 51595, and 51596

ICD-9 procedure codes: 57.71, 57.87, and 56.51

**Codes for bladder cancer**

ICD-9 diagnostic codes: 188, 188.0, 188.1, 188.2, 188.3, 188.4, 188.5, 188.6, 188.7, 188.8, 188.9, 233.7, 236.7, and 239.4

**Codes for comorbid conditions**

*ICD-9 diagnostic codes:*

- Pneumonia: 481.0, 482.0-482.4, 482.8-483.1, 483.8, 484.0-484.1, 484.3, 484.5-484.8, 485, and 486
- Surgical site infection: 997.5, 998.3, 998.50, 998.51, and 998.59
- Urinary tract infection: 599
- Pyelonephritis: 590.0, 590.1, 590.11, 590.8, and 590.81
- *Clostridium difficile:* 8.45 (9.0, 9.1—with associated metronidazole or vancomycin administration)

**References**


