

**Incidence and predictors of occult preoperative deep vein thrombosis at radical cystectomy for urothelial carcinoma**

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**Abstract**

**Introduction:** Patients undergoing radical cystectomy are at high perioperative risk for deep vein thrombosis due to age, malignancy, recent transurethral resection, and neoadjuvant chemotherapy. We, therefore, evaluated the incidence and predictors of occult preoperative deep vein thrombosis prior to radical cystectomy for urothelial carcinoma.

**Methods:** We prospectively screened 52 asymptomatic patients with urothelial carcinoma undergoing radical cystectomy at our institution with lower extremity ultrasound and D-dimer assay within two weeks prior to surgery. Patients with a prior history of deep vein thrombosis and those on systemic anticoagulation were excluded.

**Results:** We identified 4/52 patients (7.7%) with preoperative asymptomatic deep vein thrombosis prior to radical cystectomy. Median D-dimer for patients with and without preoperative deep vein thrombosis was 787 ng/ml(interquartile range [IQR] 365–1257) and 260 ng/ml(IQR 158–498), respectively. A D-dimer threshold of >250 ng/ml had a sensitivity of 100% and specificity of 50%, resulting in a negative predictive value of 100% and positive predictive value of 14.8% for preoperative deep vein thrombosis. Increasing the D-dimer threshold to >1000 ng/ml created a sensitivity of 50% and specificity of 85%, resulting in a

negative predictive value of 92% and positive predictive value of 33%. D-dimer values did not significantly vary with neoadjuvant chemotherapy or days since transurethral resection.

**Conclusions:** Approximately 8% of patients had an occult deep vein thrombosis prior to radical cystectomy. D-dimer can provide sensitive diagnostic utility for deep vein thrombosis in the pre-radical cystectomy setting and could help guide use of preoperative lower extremity ultrasound in this high-risk patient population.

## Introduction

Patients undergoing extensive intraabdominal surgery for malignancy are at increased risk of deep vein thrombosis (DVT) due to surgical trauma and inherent coagulopathy associated with malignancy<sup>1-3</sup>. Pulmonary embolism (PE) secondary to DVT is the second leading cause of death in cancer patients.

Radical cystectomy (RC) with pelvic lymph node dissection represents definitive therapy for muscle-invasive and recurrent non-muscle-invasive urothelial carcinoma of the bladder. Bladder cancer patients tend to be older, male, and frequently receive preoperative chemotherapy and undergo transurethral bladder tumor resections prior to definitive surgery<sup>4</sup>. Accordingly, RC has the highest rate of postoperative DVT within urologic surgery<sup>5</sup>, with an incidence of 3% for cystectomies performed for all indications<sup>6</sup> and up to 6% for RC performed for malignancy<sup>7,8</sup>. However, given the multiple baseline risk factors for thromboembolic events, we hypothesized that a significant number of DVTs diagnosed postoperatively may have been present before surgery.

Only one study has examined the incidence of pre-RC asymptomatic DVT, and it found an incidence of 13.0%<sup>9</sup>. It also reported a lower rate of postoperative DVT among patients with a negative preoperative DVT evaluation compared to historical controls, suggesting that progression of initially asymptomatic preoperative DVTs may account for many symptomatic DVTs identified in the post-operative period.

To our knowledge, no study has explored screening approaches for preoperative DVT before RC. Herein, we sought to prospectively assess the incidence of occult preoperative DVT before RC for urothelial carcinoma and determine the utility of pre-operative D-dimer assay and other clinical factors for identifying patients with an occult preoperative DVT.

## Methods

### *Study design*

This prospective observational study was approved by the Internal Review Board at the Mayo Clinic in Rochester, Minnesota. Oral and written informed consent was obtained from all patients. Inclusion criteria was planned RC for urothelial carcinoma between 2012 and 2015.

Exclusion criteria included history of venous thromboembolism and active anticoagulation therapy. A total of 52 patients were included.

### ***Preoperative DVT screening protocol***

The diagnosis of preoperative DVT was established using compressive duplex ultrasound (US) with Doppler including the femoral, popliteal and calf veins according to standard procedures (grey scale, B-mode, color Doppler) within two weeks of surgery. D-dimer assay was also performed for 50/52 patient at the time of US, including all patients with preoperative DVT. All patients without DVT were maintained on one month of Lovenox DVT prophylaxis postoperatively per our institutional protocol. All patients were monitored for symptomatic DVT postoperatively per standard institutional protocols.

### ***Statistical analysis***

The sensitivity, specificity, positive and negative predictive values of the D-dimer assay for preoperative DVT was calculated for our patient population. A two-tailed Mann-Whitney U-test ( $p < 0.05$  considered significant) was used to compare D-dimer values between patients receiving or not neoadjuvant chemotherapy, and regression analysis was used to assess for a relationship between time from transurethral resection of bladder tumor (TURBT) and preoperative D-Dimer value. JMP v. 10 was used for all statistical analysis.

## **Results**

### ***Baseline characteristics***

The clinical characteristics and demographic data for our patient population are displayed in Table 1. Fifty-two patients were included in our study, including 43 men and 9 women. The median age of all patients was 69 years (IQR 62.5-73) at the time of RC. 25/52 (48%) had received neoadjuvant chemotherapy.

### ***DVT incidence***

DVT was detected before RC in 4/52 patients (7.7%), all asymptomatic men. One of four patients (25%) with a preoperative DVT and 24/48 (50%) patients without preoperative DVT had received neoadjuvant chemotherapy. The four patients with asymptomatic preoperative DVT were initiated on early therapeutic anticoagulation postoperatively on an individualized basis without complication, while patients without preoperative DVT were maintained on prophylactic Lovenox for 30 days postoperatively per institutional protocol. No symptomatic postoperative DVTs were identified following RC using standard institutional surveillance.

### ***D-dimer assay***

The median D-dimer value for patients with preoperative DVT was 787 ng/ml (IQR 365-1257), while patients without preoperative DVT had a median D-dimer value of 260 ng/ml (IQR 158-

498, Table 1). A D-dimer threshold of >250 ng/ml had a sensitivity of 100% and specificity of 50%, resulting in a negative predictive value 100% and positive predictive value of 14.8% for pre-operative DVT (Figure 1). On the other hand, a D-dimer threshold of >1000 ng/ml had a sensitivity of 50% and specificity of 85%, resulting in a negative predictive value of 92% and positive predictive value of 33% for pre-operative DVT.

No significant difference was observed in D-dimer values between patients who received and did not receive neoadjuvant chemotherapy (305 ng/ml vs 270 ng/ml, respectively  $p=0.51$ , Figure 2). In patients proceeding directly from TURBT to RC, the duration between TURBT and D-dimer assay showed no significant correlation with measured D-dimer values ( $R^2=0.03$ ,  $p=0.37$ , Figure 3).

## Discussion

Our prospective study identifies a high incidence of preoperative DVT in patients undergoing RC for urothelial carcinoma. All preoperative DVT in this study were identified with routine screening and were otherwise asymptomatic. Depending on the cut-off used, the diagnostic utility of the D-dimer could be tailored to have a negative predictive value of 100% (250ng/ml threshold) or a high positive predictive value of 33% (1000ng/ml threshold). Thus, these results warrant further exploration of D-dimer in the risk stratification for pre-operative DVT before RC.

Few previous studies have reported the prevalence of preoperative DVT. Two studies dating to the 1970 and 1980s screened for DVT preoperatively in patients undergoing surgery for a broad range of diseases, and found a preoperative DVT rate ranging from 15.8 to 20%<sup>10,11</sup>. A more contemporary study by Stender *et al.* identified a preoperative DVT rate of 7.7% in patients scheduled for surgery for colorectal cancer<sup>12</sup>. Although they did not report D-dimer values, using the American Society of Anesthesiologists (ASA) Risk Score they showed a significant trend between preoperative DVT risk and increasing ASA score. Their study also found a significantly greater incidence of preoperative DVT in women compared to men, which contrasts with our study finding 4/4 preoperative DVTs in men, although our study has a smaller sample size and bladder urothelial carcinoma has a strong male predominance.

Within urology, Schomburg *et al.* recently reported a rate of subclinical preoperative DVT in RC patients of 13.9%<sup>9</sup>. RC is known to carry the highest prevalence of postoperative DVT within urologic surgery due to the advanced age, pelvic malignancy, prior chemotherapy, multiple pelvic surgical procedures and coagulopathies within the patient population<sup>13</sup>. The reported rate of postoperative symptomatic DVT after RC is between 4-6%<sup>6,7</sup>, but our data, combined with that of Schomburg *et al.*, suggest that this is a significant underestimation of the true rate of perioperative DVT within the bladder cancer patient population given the prevalence of asymptomatic DVT. Additionally, our elevated rate of preoperative DVT creates the potential

that improved preoperative screening to identify asymptomatic patients may be able to lessen the significant clinical impact of potentially catastrophic thromboembolic complications postoperatively.

We assessed the utility of the D-dimer assay relative to lower extremity US for pre-RC DVT screening given the much lower cost of the former. The D-dimer assay is an established laboratory study for screening for venous thrombosis, most notable for its excellent negative predictive value in the non-surgical setting<sup>14,15</sup>. We were reassured to find no significant association between D-dimer values and receipt of neoadjuvant chemotherapy or time from last transurethral resection, suggesting that the utility of D-dimer to predict pre-RC DVT may not be confounded by non-DVT related clinical variables in the cystectomy population. Our study found that a positive D-dimer threshold of 250 ng/ml achieved a high sensitivity and a negative predictive value of 100%, while a threshold of 1000 ng/ml had a higher specificity (85%) and a positive predictive value of 33%. These results support further study to determine if a pre-RC D-dimer of less than 250 ng/ml can obviate the need for a lower extremity US or if a pre-RC D-dimer of over 1000 ng/ml supports further evaluation with lower extremity US.

Analogous to the Wells' Criteria to risk stratify patients and augment D-dimer evaluation, we envisage future studies establishing a D-dimer-based clinical risk score for DVT before RC. This score can include other relevant variables, such as age, BMI, comorbidities, ASA or Khorana scores as previously described<sup>9,12</sup>. If validated, a pre-RC D-dimer measurement can guide the judicious use of lower extremity US and thereby become a valuable part of the preoperative evaluation in this patient population to minimize post-RC complications.

All DVTs in our study were asymptomatic both pre- and postoperatively, which brings to question their clinical significance. While future studies will be required to address this question in our patient population, significantly increased 30 and 90-day mortality has been reported associated with asymptomatic DVT and VTE in hospitalized patients<sup>16,17</sup>. Additionally, Schomburg *et al* found a trend toward lower rates of postoperative DVT compared to historical controls in the patient population that underwent preoperative screening, suggesting that a subset of asymptomatic preoperative DVTs may serve as the nidus for progression to symptomatic and clinically impactful thromboembolic events postoperatively<sup>9</sup>. These data highlight the potential for positive clinical impact of improved preoperative DVT screening in oncology patients at high risk for DVT.

## Conclusions

Our study was designed as an evaluation of the prevalence of preoperative DVT and the effectiveness of preoperative screening approaches. As such, our current study is limited by a small sample size that does not allow for robust preoperative DVT risk factor stratification or analysis of outcomes postoperatively based on the presence or absence of preoperative DVT. Our

data clearly show that preoperative DVT is a realized risk in patients with urothelial carcinoma of the bladder and argues for future studies aimed at optimizing DVT risk stratification to inform peri-operative decision making and eliminate preventable thromboembolic events in this high-risk patient population.

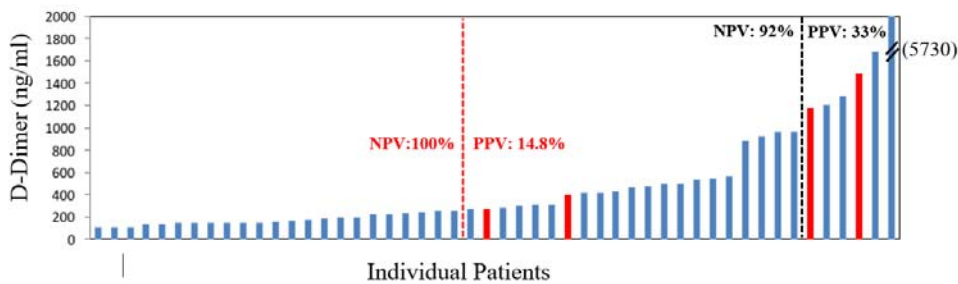
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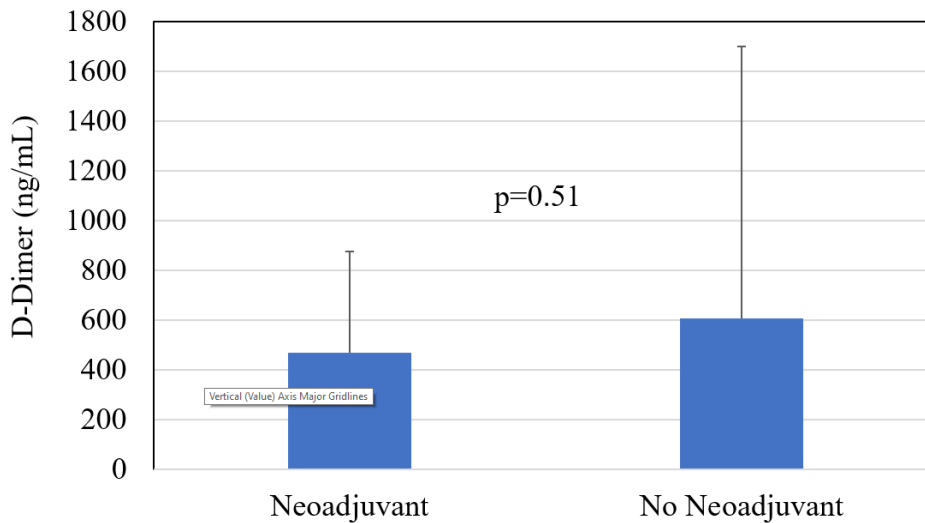
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Figures and Tables

**Fig. 1.** Distribution of D-dimer values in patients with urothelial carcinoma two weeks prior to radical cystectomy. Vertical red dashed line represents positive cutoff value of 250 ng/ml and vertical black dashed line represents positive cutoff value of 1000 ng/ml used for calculating predictive values. Red columns represent patients with preoperative deep vein thrombosis diagnosed by ultrasound. NPV: negative predictive value; PPV: positive predictive value.

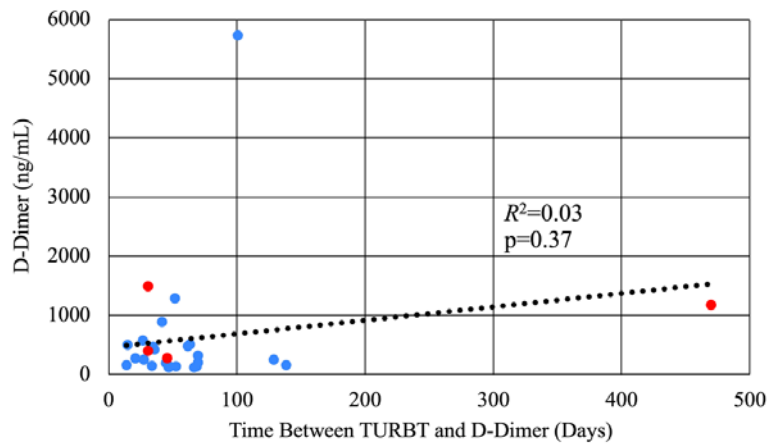


**Fig. 2.** Influence of receipt of neoadjuvant chemotherapy on the preoperative D-dimer value in patients with urothelial carcinoma two weeks prior to radical cystectomy.





**Fig. 3.** Influence of time from transurethral resection of bladder tumor (TURBT) on the preoperative D-dimer value in patients with urothelial carcinoma two weeks prior to radical cystectomy.



<b>Table 1. Baseline patient cohort demographics</b>			
	<b>DVT-positive (n=4)</b>	<b>DVT-negative (n=48)</b>	<b>Total (N=52)</b>
Age (median)	69.3	69.5	68.8
Sex, male	4/4 (100%)	39/48 (81%)	43/52 (83%)
Neoadjuvant chemotherapy	1/4 (25%)	24/48 (50%)	25/52 (48%)
Postoperative DVT	N/A	0/48	0/48
D-dimer (ng/ml, IQR)	787 (365–1257)	260 (158–498)	278 (166–522)
<b>Comorbidities</b>			
Obesity	2/4 (50%)	13/48 (27%)	15/52 (29%)
Smoker, past or present	2/4 (50%)	38/48 (79%)	40/52 (77%)
History of prior malignancy	2/4 (50%)	10/48 (21%)	12/48 (23%)
Inflammatory bowel disease	0/4 (0%)	2/48 (4%)	2/52 (4%)
Congestive heart failure	0/4 (0%)	1/48 (2%)	1/52 (2%)
Cardiac arrhythmia	0/4 (0%)	7/48 (15%)	7/52 (13%)
Hypertension	3/4 (75%)	22/48 (46%)	25/52 (48%)
COPD	0/4 (0%)	5/48 (10%)	5/52 (10%)
Diabetes mellitus type 2	1/4 (25%)	7/48 (15%)	8/52 (15%)
Renal impairment (moderate/severe)	0/4 (0%)	7/48 (15%)	7/52 (13%)
Liver disease	0/4 (0%)	0/48 (0%)	0/52 (0%)
cT $\geq 2$	1/4 (25%)	34/48 (71%)	35/52 (67%)
pT $\geq 2$	2/4 (50%)	22/48 (46%)	24/52 (46%)
pN $\geq 1$	1/4 (25%)	11/48 (23%)	12/52 (23%)

COPD: chronic obstructive pulmonary disease; DVT: deep vein thrombosis; IQR: interquartile range; N/A: not available.