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# Venous thromboembolism after radical cystectomy: Experience with screening ultrasonography

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**KEYWORDS**

Deep vein thrombosis;
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Ultrasonography;
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**ABBREVIATIONS**

BMI, body mass index;
DVT, deep vein thrombosis;
EBL, estimated blood loss;
LMWH, low-molecular weight

**Abstract** ***Objectives:*** To detect the incidence of immediate postoperative deep vein thrombosis (DVT) using screening lower extremity ultrasonography (US) in patients undergoing radical cystectomy (RC) and to determine the rate of symptomatic pulmonary embolism (PE) after RC and identify risk factors for venous thromboembolic (VTE) events in a RC population.

***Patients and methods:*** We performed a retrospective review of prospective data collected on patients who underwent RC between July 2008 and January 2012. These patients underwent screening US at 2/3 days after RC to determine the rate of asymptomatic DVT. A chart review was completed to identify those who had a symptomatic PE. Univariate and multivariable analysis was used to identify risk factors associated with DVT, PE and total VTE events.

***Results:*** In all, 221 patients underwent RC and asymptomatic DVT was identified in 21 (9.5%) on screening US. Nine (4.5%) developed symptomatic PE at a median of 9 days, of which no patients had positive lower extremity US postoperatively. Increased length of hospital stay, increased estimated blood loss, and lower body

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heparin;
LOS, length of hospital stay;
PE, pulmonary embolism;
RC, radical cystectomy;
US, ultrasonography;
VTE, venous thromboembolism

mass index were linked to risk of PE, and only a previous history of DVT was associated with postoperative DVT.

***Conclusion:*** Patients who undergo RC are at high-risk for thromboembolic events and multimodal prophylaxis should be administered. Clinicians should be especially vigilant in those who demonstrate factors associated with higher risk for VTE events.



## Introduction

In the USA, >70,000 men and women are diagnosed with bladder cancer annually and it is associated with ≈15,000 deaths [1]. The 'gold standard' for muscle-invasive and locally advanced disease is radical cystectomy (RC) with pelvic lymph node dissection [2]. Furthermore, patients with other malignancies, such as colorectal masses and gynaecological cancers, may require RC as part of their surgical plan. Unfortunately, extirpation of the bladder and creation of a urinary diversion are not without consequence, as reported 90-day complication rates range from 49% to 64% [3–5]. Mortality rates are also significant ranging from 1.5% to 6.9% [3–6].

One of the most devastating consequences of RC is venous thromboembolism (VTE), which can account for up to 22% of total deaths after surgery [5,7]. In the bladder cancer literature, symptomatic thromboembolic events occur in up to 8.3% of patients [3–6,8], but subclinical deep vein thrombosis (DVT) rates can be as high as 24.4% when examining an ultrasonography (US)-screened population [9]. In fact, undergoing a RC is a significant, independent risk factor on multivariable analysis for developing a DVT [9].

Clearly, VTE is a significant burden for patients after RC. Several studies have reported the rates of symptomatic VTE; however, few reports are available describing the 'true' incidence in a screened population. In the present study, our objective was to describe the rate of DVT in an US-screened population and to identify factors that portend increased risk. Furthermore, we determined the 90-day rate of symptomatic PE or any VTE and corresponding risk factors.

## Patients and methods

After obtaining Institutional Review Board approval, we performed a retrospective review of prospectively collected data of patients who underwent RC with urinary diversion from July 2008 to January 2012. All RCs were performed by one of two fellowship-trained urological oncologists. Standard RC was performed with pelvic lymphadenectomy. The template for lymph node dissection at our institution includes the obturator, common, external, and internal iliac lymph node packets. All patients received routine postoperative care via a collaborative care pathway for RC. Patients were followed at 3-month intervals for the first and second year, and every 6 months, thereafter. The follow-up consisted of: history and physical examination, routine laboratory tests, and radiographic evaluation. Each patient was queried at their 3 month visit about any complications, hospitalisations or concerns postoperatively. Directed imaging was performed for clinical signs of VTE.

During the course of the study, all patients underwent lower extremity Doppler US at 2/3 days after RC. At our institution, a 5–8 MHz US probe is used to evaluate for vein compressibility from the groin to the ankle including but not limited to the common and superficial femoral veins, popliteal veins and posterior tibial and peroneal veins in the calf bilaterally. In our early study population (July 2008 to October 2010), VTE prophylaxis included perioperative sequential compression devices and early ambulation. Patients found to have DVT on US were started on therapeutic dosages of heparin or low-molecular weight heparin (LMWH) followed by long-term warfarin therapy. In the later study population (October 2010 to January 2012), all patients received perioperative chemoprophylaxis with heparin or LMWH, in addition to sequential compression devices and early ambulation. Chemoprophylaxis was discontinued when patients were discharged home. Patients diagnosed with DVT in this group were also started on therapeutic dosages of anticoagulation. All patients diagnosed with symptomatic PE within 90 days were identified and included in our analysis.

Rates of asymptomatic DVT on screening US, symptomatic PE, and incidence of total VTE were determined. Potential risk factors [age, body mass index (BMI), history of DVT, neoadjuvant chemotherapy, previous abdominal surgery, operating room time, estimated blood loss (EBL), blood transfusions, chemoprophylaxis, pathological stage, and length of hospital stay (LOS)] were analysed for their association with asymptomatic DVT, symptomatic PE, and total incidence of VTE. Univariate analysis was used with chi-square and Fisher's exact test for categorical data and the independent *t*-test for continuous variables. Multivariable analysis was performed using logistic regression analysis

including forward stepwise progression analysis. Odds ratios were calculated using a 95% CI for those variables that remained statistically significant. $P$ values are two-tailed and a $P < 0.05$ is considered to indicate statistical significance. SPSS version 10 was used for all analyses.

## Results

Between July 2008 and January 2012, 221 patients underwent RC. This includes all patients who had RC for urological cancers as well as colorectal and gynaecological cancers, and even one patient who had a hemicorpectomy for a sacral mass. All patients had screening lower extremity US at 2/3 days after RC. Baseline descriptive demographics and rates of VTE are given in Table 1. The mean (SD) age of all patients was 64.9 (9.9) years, fourteen patients (6%) had a history of prior DVT and the average hospital stay was 9.2 days. In all, 20 (9%) patients were found to have an asymptomatic DVT on postoperative screening US. Nine (4%) patients developed a symptomatic PE at a median (range) of 9 (2–22) days. Five patients developed PE after discharge home. None of the patients who developed symptomatic PE were found to have DVT on postoperative screening US at day 2/3.

Univariate analysis was performed and identified a history of DVT and LOS as being associated with a positive screening lower extremity US. Blood transfusion, BMI, EBL, and LOS were associated with symptomatic PE; while EBL, transfusions, and LOS correlated with total VTE events (Table 1). Interestingly, medical VTE prophylaxis did not confer a decreased risk of DVT at postoperative screening US or symptomatic PE (data not shown). Upon multivariable analysis (Table 2), history of DVT was the only risk factor associated with a positive screening US. BMI, EBL, and LOS correlated with symptomatic PE; while history of DVT, pathological stage, and EBL were associated with all VTEs.

## Discussion

VTE after RC is a serious health concern and identifying patients at highest risk is paramount. Our present data suggest that patients with a previous history of DVT are at highest risk of postoperative DVT upon screening US. Furthermore, patients with decreased BMI, higher EBL, and increased LOS are at higher risk of symptomatic PE in the postoperative period. When examining all VTEs, patients with a history of DVT, higher pathological stage (pT3–4), and increased EBL were at highest risk. We found that decreased BMI conferred a higher risk of PE, which is different from other reports. Interestingly, chemoprophylaxis with heparin and LMWH was not a significant factor on univariate or multivariable analysis. Potentially, this is due to the low number of total events in both populations or that patients with a history of DVT presented at the time of RC with existing sub-clinical DVT and therefore, chemoprophylaxis did not alter the incidence at postoperative US. Furthermore, patients in the non-chemoprophylaxis group diagnosed with DVT at screening US were started on therapeutic anticoagulation and may have decreased the rate of subsequent PE, thereby, further decreasing the number of events. Regardless, perioperative chemoprophylaxis should be considered standard and initiated in all patients undergoing RC, which is the universally accepted practice [10].

In addition to perioperative chemoprophylaxis while in the hospital, it has become accepted practice to continue therapy beyond the hospital stay including up to 30 days postoperatively. In our patient population, the median (range) day of symptomatic PE was 9 (2–22) days and five of the nine patients developed PE after hospital discharge. This practice is supported by randomised controlled trials and is currently recommended by both the American Society of Clinical Oncology (ASCO) and the American College of Chest Physicians (ACCP) for patients undergoing abdominal and pelvic surgery for cancer [11–13]. Despite these recommendations, up to 77% of patients following major cancer surgery are discharged without a prescription for chemoprophylaxis [14]. A major concern for urological surgeons is the risk of intraoperative haemorrhage, postoperative haematomas, and lymphocoeles. Prostate cancer literature lends data for this setting but the results are conflicting. Koch *et al.* [15] reported a slightly increased risk of lymphocoele and haematoma, while Sieber *et al.* [16] did not find any difference in intraoperative blood loss or lymphocoele. In our present series, there were no bleeding complications or symptomatic lymphocoeles associated with chemoprophylaxis. Furthermore, transfusion rates did not differ between the two groups (data not shown).

Our present DVT rate of 9.5% and PE rate of 4.1% are similar to other groups who have reviewed their experience with morbidity after RC [3–6]. However, compared with another study of 86 patients who underwent RC and had routine screening lower extremity US, our present rate was lower (9.5% vs. 24.4%) [9]. This discrepancy may be that Clement *et al.* [9] obtained US at postoperative day 7 compared with day 2 or 3 as in our present cohort. Even these numbers may underestimate the true incidence as over one-quarter of patients will develop VTE > 14 days postoperatively and 17% of all VTE events occur after discharge [8,17]. Ours is the largest series to date of patients who have undergone routine Doppler US of the lower extremities after RC and may represent the 'truest' rate of DVT immediately after surgery. Clearly, this patient

**Table 1** Baseline characteristics and univariate analysis of factors associated with VTE.

| | DVT on screening US | | *P* |
|---|---|---|---|
| Variable | Yes ($n$ = 20) | No ($n$ = 201) | |
| Gender, $n$ (%) | | | NS |
| Male | 17 (10) | 151 (90) | |
| Female | 3 (6) | 50 (94) | |
| Mean (SD): | | | |
| Age, years | 65 (11.3) | 65 (9.9) | NS |
| BMI, kg/m$^2$ | 27.8 (5.3) | 28.2 (5.5) | NS |
| Operating room time, min | 516 (280) | 479 (214) | NS |
| EBL, mL | 787 (1009) | 711 (476) | NS |
| LOS, days | 7.9 (6) | 9.3 (5) | < 0.01 |
| Neoadjuvant chemotherapy, $n$ (%) | | | NS |
| Yes | 8 (14) | 51 (86) | |
| No | 12 (7) | 150 (93) | |
| Urinary diversion, $n$ (%) | | | NS |
| Ileal conduit | 9 (7) | 129 (93) | |
| Neobladder | 11 (13) | 71 (87) | |
| History of pelvic surgery, $n$ (%) | | | NS |
| Yes | 7 (9) | 69 (91) | |
| No | 13 (9) | 132 (91) | |
| Pathological stage, $n$ (%) | | | NS |
| T0,Ta, T1, Tis | 6 (8) | 66 (92) | |
| T2 | 7 (12) | 50 (88) | |
| T3 | 6 (11) | 47 (89) | |
| T4 | 1 (3) | 38 (97) | |
| Node status, $n$ (%) | | | NS |
| Positive | 6 (11) | 47 (89) | |
| Negative | 14 (8) | 154 (92) | |
| Chemoprophylaxis, $n$ (%) | | | NS |
| Administered | 7 (8) | 81 (92) | |
| Not Administered | 13(10) | 120 (90) | |
| History of DVT, $n$ (%) | | | < 0.01 |
| Yes | 4 (29) | 10 (71) | |
| No | 16 (8) | 191 (92) | |
| Number of transfusions, $n$ (%) | | | NS |
| 0 | 14 (10) | 133(90) | |
| 1 | 0 | 21 (100) | |
| 2 | 2 (6) | 31 (94) | |
| 3 or more | 4 (20) | 16 (80) | |
| | Symptomatic PE | | |
| | Yes ($n$ = 9) | No ($n$ = 212) | |
| Gender, $n$ (%) | | | NS |
| Male | 7 (4) | 161 (96) | |
| Female | 2 (4) | 50 (96) | |
| Mean (SD): | | | |
| Age, years | 67 (7.6) | 65 (10.1) | NS |
| BMI, kg/m$^2$ | 25 (4.2) | 28 (5.5) | 0.04 |
| OR time, min | 510 (227) | 481(221) | NS |
| EBL, mL | 1027 (462) | 685 (553) | < 0.01 |
| LOS, days | 15 (13) | 8 (4.5) | < 0.01 |
| Neoadjuvant chemotherapy, $n$ (%) | | | NS |
| Yes | 2 (3) | 57 (97) | |
| No | 7 (4) | 154 (96) | |
| Urinary diversion, $n$ (%) | | | NS |
| Ileal conduit | 5 (4) | 132 (96) | |
| Neobladder | 4 (5) | 78 (95) | |

**Table 1** (*continued*)

| | Symptomatic PE | | |
|---|---|---|---|
| History of pelvic surgery, *n* (%) | | | NS |
| Yes | 5 (3) | 139 (97) | |
| No | 4 (5) | 72 (95) | |
| Pathological stage, *n* (%) | | | NS |
| T0,Ta, T1, Tis | 1 (1) | 71 (99) | |
| T2 | 2 (4) | 55 (96) | |
| T3 | 4 (8) | 49 (92) | |
| T4 | 2 (5) | 36 (95) | |
| Node status, *n* (%) | | | NS |
| Positive | 4 (8) | 49 (92) | |
| Negative | 5 (3) | 162 (97) | |
| Chemoprophylaxis, *n* (%) | | | NS |
| Administered | 3 (3) | 85 (97) | |
| Not Administered | 6 (5) | 126 (95) | |
| History of DVT, *n* (%) | | | NS |
| Yes | 1 (7) | 13 (93) | |
| No | 8 (4) | 198 (96) | |
| Number of transfusions, *n* (%) | | | 0.03 |
| 0 | 4 (3) | 143 (97) | |
| 1 | 0 (0) | 21 (100) | |
| 2 | 3 (9) | 30 (91) | |
| 3 or more | 2 (11) | 17 (89) | |
| | All VTE events | | |
| | Yes ($n = 29$) | No ($n = 192$) | |
| Gender, *n* (%) | | | NS |
| Male | 23 (14) | 145 (86) | |
| Female | 6 (11) | 47 (89) | |
| Mean (SD): | | | |
| Age, years | 64 (10.4) | 65 (9.9) | NS |
| BMI, kg/m$^2$ | 27 (5.1) | 28 (5.6) | NS |
| OR time, min | 517 (267) | 477 (213) | NS |
| EBL, mL | 1008 (891) | 676 (473) | $<0.01$ |
| LOS, days | 11 (9.4) | 9 (4.3) | 0.03 |
| Neoadjuvant chemotherapy, *n* (%) | | | NS |
| Yes | 10 (17) | 48 (83) | |
| No | 19 (12) | 144 (88) | |
| Urinary diversion, *n* (%) | | | NS |
| Ileal Conduit | 15 (11) | 124 (89) | |
| Neobladder | 14 (17) | 68 (83) | |
| History of pelvic surgery, *n* (%) | | | NS |
| Yes | 10 (13) | 66 (87) | |
| No | 19 (13) | 126 (87) | |
| Pathological stage, *n* (%) | | | NS |
| T0,Ta, T1, Tis | 9 (11) | 70 (89) | |
| T2 | 8 (14) | 49 (86) | |
| T3 | 9 (17) | 44 (83) | |
| T4 | 3 (9) | 29 (91) | |
| Node status, *n* (%) | | | NS |
| Positive | 9 (19) | 38 (81) | |
| Negative | 20 (11) | 154 (89) | |
| Chemoprophylaxis, *n* (%) | | | NS |
| Administered | 19 (19) | 79 (81) | |
| Not Administered | 10 (8) | 113 (92) | |
| History of DVT, *n* (%) | | | NS |

(*continued on next page*)

**Table 1** (*continued*)

| | All VTE events | | |
|---|---|---|---|
| Yes | 5 (33) | 10 (67) | |
| No | 24 (12) | 182 (88) | |
| Number of transfusions, *n* (%) | | | 0.04 |
| 0 | 18 (12) | 129 (88) | |
| 1 | 1 (5) | 20 (95) | |
| 2 | 4 (12) | 29 (88) | |
| 3 or more | 6 (30) | 14 (70) | |

NS, not statistically significant.

**Table 2** Multivariable analysis of factors associated with VTE.

| Variable | Odds ratio (95% CI) | *P* |
|---|---|---|
| DVT on screening US | | |
| History of DVT | 8.73 (1.6–4.7) | 0.01 |
| LOS | | NS |
| Symptomatic PE | | |
| LOS | 1.4 (1.09–1.8) | < 0.01 |
| EBL | 1.002 (1.0002–1.005) | 0.03 |
| BMI | 0.63 (0.41–0.97) | 0.04 |
| Number of transfusions | | NS |
| All VTE events | | |
| History of DVT | 7.68 (1.51–38.8) | 0.01 |
| EBL | 1.001 (1.0003–1.002) | 0.01 |
| LOS | 1.4 (1.1–1.8) | < 0.01 |
| Number of transfusions | | NS |

NS, not statistically significant.

population is at very high risk of VTE and extreme vigilance should be practiced.

Not only are VTEs a significant risk for morbidity and mortality after RC, they also pose a significant financial burden. It is estimated that DVT and PE garner a cost ranging from 7.5 to 39.5 billion American dollars annually [18]. The Agency for Healthcare Research and Quality (AHRQ) estimates the incremental inpatient cost to be $10,000 per DVT and $20,000 per PE [19]. In addition, it is estimated that the vast majority of these may be preventable, and if prevented, would result in healthcare savings of 3.4–27 billion dollars/year. VTE is one of the most common preventable causes of inpatient mortality, making prophylaxis critical in high-risk patients [19,20]. Patients who undergo RC should be considered 'highest risk' and multifaceted DVT prophylaxis should be considered for both patient and financial factors.

There are limitations to our present study. First, the significance of subclinical DVT identified on screening US postoperatively is not completely understood. We also acknowledge that not all patients with subclinical DVT will progress to clinical PE, making the relevance of identification on screening questionable. It is also important to note that the accuracy of lower extremity Doppler US for the diagnosis of DVT in asymptomatic patients is unknown. The use of venous US for the diagnosis of symptomatic proximal lower extremity DVT has a reported sensitivity and specificity of 97% and 94%, respectively, although this is very operator dependent [21]. It is also important to understand that not all DVTs have the potential for PE and that even when PE is definitively present, detectable lower extremity DVT by compression US is only found in 50% of patients [22]. However, our objective in the present study was to identify the 'actual' rate of DVT after RC and identify factors that may place patients at higher risk, which our study accomplishes. Second, our present patient population did not undergo preoperative Doppler US of the lower extremities to identify patients who underwent RC with a pre-existing subclinical DVT. As our present data suggest, patients with a previous history of DVT were at increased risk of postoperative VTE. Clearly, these patients may have had existing DVT before surgery. Furthermore, follow-up US were not obtained past the immediate postoperative setting and the rate of delayed subclinical DVT formation is unknown. Third, while this is the largest series of patients undergoing screening US postoperatively after RC, the limited number of patients and events may have been inadequate to demonstrate all critical risk factors associated with VTE. Namely, chemoprophylaxis was not found to be significant in our patient population. Potential reasons for this are previously mentioned in our report. As indicated, multi-faceted VTE prophylaxis is necessary in the RC population and perioperative chemoprophylaxis up to 30-days postoperatively along with sequential compression devices during the entire hospital course should be encouraged.

## Conclusion

All patients who undergo RC should be considered for multimodal VTE prophylaxis perioperatively. Clinicians should be especially vigilant in those patients who

demonstrate factors that confer higher risk and prolonged (30 day) thromboembolism prophylaxis should be considered.

## Conflicts of interest

There are no conflicts of interest with any of the authors of the manuscript.

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None.

## Informed consent

This review was approved by the Institutional Review Board and Informed Consent was deemed not necessary as it was exempt because of the retrospective design.

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