

## Review

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# Thromboembolism in Patients with Bladder Cancer: Incidence, Risk Factors and Prevention

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**Abstract.** Patients with bladder cancer are at high risk of developing both venous and arterial thromboembolic events. Factors that contribute to this phenomenon include the hypercoagulable state induced by the malignancy itself, medical comorbidities that are common in this predominantly elderly patient population as well as treatments such as prolonged pelvic surgery and cisplatin-based chemotherapy. While formal guidelines address prevention of venous thromboembolism in patients undergoing radical cystectomy, consensus regarding the role of pharmacologic prophylaxis in patients with bladder cancer being treated with chemotherapy, either with neoadjuvant or adjuvant intent in conjunction with radical cystectomy, as part of bladder preservation protocols or for metastatic disease, has proved elusive. The present narrative review was undertaken to define the incidence of and identify risk factors for thromboembolism among patients with bladder cancer, as well as to assess the efficacy of pharmacologic prophylaxis in reducing the risk of thromboembolism in this patient population.

**Keywords:** Bladder cancer, cystectomy, cisplatin, thromboembolism

## INTRODUCTION

It has long been recognized that malignancy induces a hypercoagulable state that significantly increases the risk of developing both venous and arterial thromboembolism (VTE and ATE, respectively). Among solid organ malignancies, bladder cancer is associated with a particularly high VTE risk, with the incidence rate being as high as 7.9 events per 100 patient-years in those with metastatic disease [1]. The risk of VTE among bladder cancer patients has been shown to be highest within the first six months of diagnosis [2], a finding that is at least partially explained by the risk imparted by major pelvic surgery, namely radical cystectomy (RC), which is

the primary treatment for localized, muscle-invasive bladder cancer.

Recently, the contribution of systemic chemotherapy to the heightened risk of thromboembolism (TE) among patients with cancer has begun to be elucidated. Cisplatin is widely used in conjunction with either gemcitabine (GC) or methotrexate, vinblastine and adriamycin (MVAC) in patients with urothelial carcinoma (UC) of the bladder, both for treatment of metastatic disease as well as neoadjuvant or adjuvant therapy in those treated with RC and pelvic lymph node dissection (PLND). Cisplatin-based regimens have been shown to be associated with a higher risk of VTE and possibly ATE compared to non-cisplatin-based regimens [3, 4]. Cisplatin exerts a potent thrombogenic effect, likely by damaging the endothelial lining of blood vessels as well as by inducing platelet activation [5, 6].

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The objectives of the present narrative review were to summarize our current understanding of the incidence of and risk factors for TE among patients with bladder cancer, as well as to present the evidence for a benefit of pharmacologic prophylaxis in reducing the risk of VTE in this population.

### **INCIDENCE AND PROGNOSTIC IMPLICATIONS OF THROMBOEMBOLISM IN PATIENTS WITH BLADDER CANCER**

Malignancy is a significant risk factor for VTE, with the odds of a concomitant cancer diagnosis being over seven times higher among patients diagnosed with DVT and/or PE than age-matched controls [7]. Of all VTE events, approximately 20–30% occur in the setting of malignancy [8–10]. The incidence of VTE among patients with cancer appears to be rising [11], which is likely attributable to longer survival as well as increased use of cross-sectional imaging, central venous catheters and other invasive diagnostic and therapeutic procedures.

Several large population-based studies have reported a high incidence of VTE among patients with bladder cancer. Among a Dutch cohort of 2,250 patients, the incidence of VTE was found to increase from 0.4 events per 100 patient-years in the 12 months prior to diagnosis to 1.3 events per 100 patient-years in the first six months after diagnosis [12]. The incidence was highest among patients with metastatic disease, with a rate of 3.1 events per 100 patient-years. In a study of 24,861 bladder cancer cases in the California Cancer Registry, the reported two-year cumulative incidence of VTE was 1.9%, which was fivefold higher than that in the general population [2]. The risk was highest in the first six months after diagnosis, during which time the incidence rate was 2.5 events per 100 patient-years compared to 1.0 events per 100 patient-years in the ensuing six months. Among patients with metastatic disease, the cumulative two-year incidence of VTE was 6.3%, with incidence rates of 15.3 per 100 patient-years and 4.9 per 100 patient-years in the first six months and second six months after diagnosis, respectively. Another study reported an incidence rate of 7.9 events per 100 patient-years in patients with metastatic bladder cancer [1].

Although VTE events are the most common type of TE events occurring in patients with cancer, recent evidence suggests that the risk of ATE is also ele-

vated in the setting of malignancy. In an analysis of the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database of 17,637 pairs of patients with cancer and matched controls, the six month cumulative incidence of ATE was 4.7% among patients with cancer compared to 2.3% among those without a cancer diagnosis [13]. The cumulative incidence rose to 7.1% and 4.5% at one year and 10.4% and 8.5% at two years, respectively, suggesting that the excess risk of ATE becomes attenuated over time.

The mechanisms by which malignancy induces a hypercoagulable state have been reasonably well-elucidated. The principal mechanism involves tissue factor (TF), a transmembrane glycoprotein that localizes coagulation factor VII/VIIa to the cell surface and activates the clotting cascade. TF is expressed on cancer cells as well as cancer cell-derived microparticles, which are vesicular structures released by multiple cell types and whose membranes retain the protein structures of their parent cells [14]. Bladder cancer patients who undergo RC and are found to have TF-positive tumors have a three-fold higher risk of dying from their disease than TF-negative patients [15]. Cancer-induced inflammation can further increase TF expression by host inflammatory cells [16]. Heparanase, a protease that degrades the heparin sulfate component of extracellular matrix, has also been implicated in the procoagulant effect of cancer. Overexpression of heparanase has been shown to be more common in patients with high-grade, locally advanced and metastatic bladder tumors [17].

The association between malignancy and TE may also be explained by shared risk factors, including age, smoking and obesity, with systemic chemotherapy, surgery and other invasive procedures further compounding this risk. Frequent use of cross-sectional imaging in cancer patients also results in detection of asymptomatic TE, particularly PEs on chest CT scans done for staging purposes.

The occurrence of TE during the disease course of patients with cancer has been shown to be associated with a worse prognosis. This is partly explained by the fact that patients who present with or develop TE after diagnosis are more likely to have distant metastases and therefore worse cancer-specific survival [18]. Even among patients with clinically localized, muscle-invasive bladder cancer, however, the occurrence of VTE portends a higher likelihood of cancer progression and cancer-related mortality [19], which suggests that VTE may be a manifesta-

tion of occult metastatic disease. Interestingly, both TF and heparanase have been shown to be involved in cancer invasion and metastasis through their degradative actions on the extracellular matrix [20], with TF-factor VIIa signaling having been shown to upregulate the production of several matrix metalloproteinases that break down extracellular matrix [21]. TE events are also directly associated with considerable morbidity and a clinically significant risk of mortality. Patients with cancer who develop DVT are at risk of PE as well as bleeding complications related to anticoagulation, both of which can result in fatality in a small proportion of patients [22]. Development of VTE in cancer patients is also associated with a significant increase in all-cause hospitalizations and a greater than \$30,000 increase in total health care costs [23].

#### **INCIDENCE OF AND RISK FACTORS FOR THROMBOEMBOLISM IN PATIENTS UNDERGOING RADICAL CYSTECTOMY**

The preponderance of studies pertaining to TE risk among patients with bladder cancer have focused on the risk of VTE in the immediate postoperative period among patients with localized, muscle-invasive disease undergoing RC and PLND. Data from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) revealed that among 43,808 patients undergoing eleven different major oncologic surgeries, the risk of developing any VTE event within 30 days of surgery among patients undergoing radical cystectomy (4.9%) was exceeded only by that of patients undergoing esophagectomy (7.3%) [24]. A population-based study of 1,641 patients undergoing RC in the UK reported that 2.9% of patients were readmitted with VTE within 12 months of surgery [25]. In another population-based study using the California Patient Discharge Data Set, the reported incidence of VTE within three months of surgery was 3.7% [26], while a study employing a commercial database of privately-insured patients reported a VTE incidence of 10% within three months of surgery [27]. Studies published by two high-volume academic centers reported 90-day DVT incidences of 3.5% and 2.1% and 90-day PE incidences of 1.8% and 2.6%, respectively [28, 29]. Meanwhile, a systematic review that included 223 studies with a total of 1,115,634 patients reported the incidence of DVT and PE after cystectomy to be 2.1% and 1.6%, respectively, with

a case fatality rate among patients who developed a PE of 44% [30].

The heterogeneity in the reported risk of VTE among different studies is likely attributable to differences in risk factors among the populations studied as well as differences in the use of pharmacologic prophylaxis. In a recent systematic review of nine open RC series, Tikkinen et al. incorporated these factors into a meta-analysis to define the baseline risk of VTE in the absence of pharmacologic prophylaxis stratified by the presence or absence of patient risk factors [31]. The reported risk of developing VTE without prophylaxis was 2.9%, 5.8% and 11.6% among patients at low (no risk factors), intermediate (age > 75 years, BMI  $\geq$  35 kg/m<sup>2</sup> and/or VTE in a first-degree relative) and high risk (prior VTE or any combination of two or more risk factors), respectively. Meanwhile, the risk of bleeding requiring reoperation was only 0.3%. Another potential source of differences in the reported risk of VTE across studies is differences in the use of imaging to screen for DVT and PE in the postoperative period, since many VTE events are asymptomatic. For example, in a French study of 86 patients who underwent RC and postoperative screening Doppler ultrasound of the legs irrespective of the presence of symptoms, 20% were found to have a DVT despite the use of pharmacologic prophylaxis [32]. Differences in imaging use likewise also explain the higher VTE risk reported by studies performed in the U.S. (4.5%) versus those performed in other westernized and non-westernized countries (3.4% and 2.5%, respectively) [30].

#### **PREVENTION OF THROMBOEMBOLISM AFTER RADICAL CYSTECTOMY**

The previously quoted baseline VTE risk of 2.9% to 11.6% means that most patients undergoing RC fall into either the moderate (3–6%) or high (>6%) VTE risk categories as defined by the American College of Chest Physicians (ACCP) clinical practice guidelines [33]. Furthermore, because the risk of major bleeding, defined as bleeding requiring surgical intervention or resulting in mortality, is low (<1%), the benefits of pharmacologic VTE prophylaxis in this patient population outweigh the risks such that all patients undergoing RC should receive either unfractionated heparin or low-molecular-weight heparin (LMWH) postoperatively. Despite strong evidence for a favorable risk-benefit ratio for pharmacologic prophylaxis, adherence to these recommendations appears to be

suboptimal, with a recent survey of 1,210 American Urological Association (AUA) members showing that 39% and 29% of respondents did not routinely use pharmacologic VTE prophylaxis after RC in low and high-risk patients, respectively [34].

The optimal duration of pharmacologic VTE prophylaxis after RC is a matter of continued debate. It is evident that a significant proportion of VTE events among patients undergoing RC occur after discharge. In a study of the ACS-NSQIP database, 6% of patients developed VTE within 30 days of surgery and 55% of VTE events were reported to occur after discharge from hospital, with the mean time from surgery to VTE diagnosis being 15 days [35].

Level one evidence for a benefit of extended pharmacologic prophylaxis after major oncologic surgery exists. In the ENOXACAN II study, a multicenter, randomized, double-blind clinical trial that enrolled patients undergoing curative open surgery for abdominal or pelvic cancer, patients randomized to at least 28 days of enoxaparin had a significantly lower risk of VTE (4.8% vs. 12.0%) than those who received only 6–10 days of prophylaxis [36]. Although criticized for its radiological rather than clinical primary endpoint (patients underwent bilateral leg venography or ultrasonography between days 25 and 31 postoperatively or sooner if symptomatic), the trial confirmed that there is a significant benefit to extended pharmacologic prophylaxis in this patient population. Accordingly, the ACCP recommends four weeks of postoperative prophylaxis for all abdominal and pelvic cancer surgery patients at high risk of VTE [33]. Although no randomized trials of extended pharmacologic prophylaxis have been performed exclusively in patients undergoing RC, a high-volume center recently reported a decrease in the postoperative VTE incidence from 12% to 5% since the institution of an extended VTE prophylaxis protocol [37].

Although the ENOXACAN II trial reported no statistically significant increase in risk of bleeding complications among patients who received extended LMWH, extended prophylaxis is not without risks. Deterioration of renal function is common in the postoperative period, with one study reporting that 13% of patients experienced a decline in eGFR to below 30 mL/min/1.73 m<sup>2</sup>, which could result in supra-therapeutic LMWH levels [38]. The cost of LMWH can also be prohibitive and is often not covered by private insurance plans and single-payer systems. Because of these issues, as well as poor awareness of the need for and efficacy of extended prophylaxis, its

utilization among patients with bladder cancer undergoing RC, while not formally reported, is expected to be low.

There is also evidence to suggest that the elevated risk of VTE among patients undergoing RC may extend beyond one month after surgery. In a study of 3,879 patients undergoing RC in the province of Ontario, 1.8% were diagnosed with VTE between 30 and 90 days of surgery [39]. Meanwhile, the previously quoted study employing the MarketScan database reported that of the 10% of patients who developed a VTE within 90 days of surgery, one-third were diagnosed between days 31 and 90 [27]. Further research is necessary to define the risk-benefit ratio of extending pharmacologic prophylaxis beyond one month after RC.

There is also emerging evidence for a benefit of early and frequent ambulation in the postoperative period for decreasing the risk of VTE after RC. In a small clinical trial in which 101 patients undergoing RC were randomized to an enhanced recovery after surgery (ERAS) protocol or usual care, the incidence of VTE was 0% in the ERAS group versus 8% in the reference group [40]. Although it must be noted that VTE was not the primary outcome of the trial, the reported difference was statistically significant.

#### **INCIDENCE OF AND RISK FACTORS FOR THROMBOEMBOLISM IN PATIENTS WITH BLADDER CANCER UNDERGOING CHEMOTHERAPY**

Cisplatin-based chemotherapy is used extensively in patients with UC of the bladder, both as an adjunct to RC and PLND in those with localized and locally-advanced but non-metastatic disease and as first-line therapy in those with regional lymph node or distant metastases. The past decade has brought increased understanding of the vascular toxicity associated with chemotherapy. Of all chemotherapeutic agents, cisplatin appears to be one of the most thrombogenic. Cisplatin-based regimens have been shown to be associated with an increased risk of VTE compared to non-cisplatin-based regimens in patients with solid organ malignancies, with a recent meta-analysis of randomized trials comparing cisplatin to non-cisplatin-based regimens finding that patients who received cisplatin had a 67% higher risk of developing VTE [3]. A related meta-analysis also showed a non-statistically-significant increased risk of ATE [4]. Cisplatin is thought to induce endothelial dam-

age by caspase-associated cell necrosis [5], which by exposing TF to its ligand factor VII activates the extrinsic coagulation pathway. A direct effect on platelet activation by direct or indirect activation of phospholipase A2 has also been proposed [6].

The absolute risk of VTE among patients receiving cisplatin-based chemotherapy is likely several-fold higher than that among even the highest-risk patients undergoing major pelvic surgery. In a study of 932 patients treated with cisplatin-based chemotherapy at a single high-volume center, 169 (18.1%) developed TE during treatment or in the four weeks following completion of therapy [41]. DVT alone was the most common event, occurring in 50% of patients, while PE alone was seen in 25%, DVT plus PE in 14%, ATE alone in 8% and DVT plus ATE in 3%. The significantly elevated risk of TE during treatment with cisplatin-based chemotherapy has been shown to apply to patients receiving treatment for bladder cancer. An analysis of the SEER-Medicare linked database reported a 19.8% incidence of VTE in the first year after diagnosis among patients receiving platinum-based chemotherapy vs. 11.6% among those who did not receive chemotherapy [42]. Both cisplatin and carboplatin-based regimens were associated with an increased VTE risk. An analysis of the Retrospective International Study of Cancers of the Urothelium (RISC), which included 1,762 patients with metastatic UC, of whom 1,337 received chemotherapy, showed a cumulative incidence of VTE of 9.6% and 3.2% among patients treated with and without chemotherapy, respectively [43]. On multivariate analysis, receipt of chemotherapy (but not type of chemotherapy regimen), pre-existing cardiovascular disease, moderate to severe renal dysfunction and variant histology were associated with an increased risk of VTE. Meanwhile, a population-based study of 2,001 bladder cancer patients treated with chemotherapy reported a VTE incidence of 8.2% within 12 months of treatment initiation [44]. A recent meta-analysis of 62 studies that included a total of 5,082 patients with bladder cancer receiving systemic therapy (with 47 of the 62 studies employing a platinum-based regimen) reported a pooled VTE rate of 5.4%. The reported incidences of DVT and PE, which were derived from different sets of studies than that for VTE, were 2.9% and 2.9%, respectively, with the reported risk of fatal PE being 0.5% [45]. The lower VTE risk reported by this meta-analysis compared to the studies referenced above can likely be attributed to the fact that the majority of the studies included in the meta-analysis were clinical trials,

which tend to enroll relatively young and healthy patients with a relatively low baseline risk of VTE.

The vast majority of studies published to date reporting VTE risk among bladder cancer patients receiving systemic therapy have predominantly included patients receiving induction chemotherapy for metastatic disease. However, recent evidence suggests that the elevated risk of TE also applies to patients with clinically localized disease receiving chemotherapy with neoadjuvant intent. Neoadjuvant chemotherapy (NCT) has been shown to confer a significant survival benefit among patients with muscle-invasive UC [46]. Furthermore, its use appears to be increasing [47], underlining the importance of defining the risk of VTE in this setting. A retrospective analysis of 202 consecutive patients with muscle-invasive UC demonstrated that NCT was associated with the development of VTE (HR 2.40, 95% CI 0.92, 6.27,  $p=0.07$ ) [19]. In this series, eight of 42 patients (19.1%) treated with NCT and RC and nine of 160 patients (5.6%) treated with RC alone developed TE. None of the events were fatal, although some resulted in treatment delays, and only one patient required insertion of an inferior vena cava (IVC) filter. In a follow-up multi-institutional study of 761 patients treated with NCT at ten institutions, the overall incidence of TE events in patients undergoing NCT was 13.8%, with a variation of 5.4% to 32.1% among institutions [48]. This variation was attributed to different institutional practices of restaging imaging post-NCT, since a significant proportion of TE events were detected incidentally as asymptomatic PE on restaging CT scans of the chest. Nevertheless, detection of asymptomatic PE is likely important as it may have a similar impact on morbidity and mortality as symptomatic PE [49]. In this series, most VTE events were isolated DVTs (49%) while 37% developed a PE. In a similar study of 357 patients treated with preoperative chemotherapy at Memorial Sloan Kettering Cancer Center (MSKCC), the reported incidence of TE from the time of commencement of chemotherapy to 90 days after RC was 22%, with 16% of patients experiencing a preoperative TE event and another 6% experiencing an event within 90 days of surgery [50]. Occurrence of TE was not associated with the probability of completing chemotherapy, time interval from chemotherapy completion to surgery or perioperative outcomes such as estimated blood loss, blood transfusion, length of stay or perioperative complications. Unlike in the previously quoted multi-institutional study, 58% of patients in the MSKCC series who developed a pre-

operative VTE required IVC filter insertion, which likely speaks to differences in institutional practices in VTE management. The increase in TE risk among patients receiving NCT does not appear to extend into the postoperative period [35]. Interestingly, although prior randomized trials of NCT reported low TE rates, a recent phase II trial of neoadjuvant dose-dense gemcitabine and cisplatin in patients with muscle-invasive UC of the bladder was closed prematurely after reporting a 23% incidence of TE events [51].

To the best of our knowledge, there are no reports on the incidence or implications of TE in patients with muscle-invasive UC who are treated with bladder-sparing protocols. In principle, one can assume that in this typically elderly patient population with multiple comorbidities that is treated with a combination of chemotherapy and radiation, TE events are not an infrequent complication. Interestingly, one of the previously referenced meta-analyses raised the possibility of an association between receipt of radiation therapy and risk of VTE in patients with bladder cancer treated with chemotherapy [45].

### **PREVENTION OF THROMBOEMBOLISM DURING TREATMENT WITH CHEMOTHERAPY**

The high incidence of VTE among bladder cancer patients receiving chemotherapy has raised the question of whether pharmacologic prophylaxis should be administered during treatment. Although no clinical trials have assessed the benefits and risks of pharmacologic VTE prophylaxis exclusively in patients with bladder cancer, patients with bladder cancer have been included in one large randomized trial exploring the role of VTE prophylaxis during treatment with chemotherapy. The SAVE-ONCO trial, a randomized, double-blind clinical trial that enrolled 3,212 patients with locally advanced or metastatic solid organ malignancy (63 of which had bladder cancer) and randomized them to a novel ultra-low-molecular-weight heparin (semuloparin) or placebo, reported a 64% relative reduction in the hazard of symptomatic DVT, non-fatal PE or death due to VTE among patients receiving prophylaxis [52]. However, the incidence of VTE was 3.4% in the placebo group and 1.2% in the semuloparin group, such that the difference in the absolute risk of VTE was only 2.2%. The PROTECHT trial, which also enrolled patients with metastatic or locally advanced solid organ tumors, randomized 779 patients to nadroparin,

a LMWH, and 387 patients to placebo. This trial, which did not enroll any patients with bladder cancer, similarly showed a statistically significant 1.9% absolute risk reduction (2.0% vs. 3.9%) in VTE risk with prophylaxis [53].

In spite of the significant relative risk reduction conferred by LMWH therapy, the ACCP and American Society of Clinical Oncology (ASCO) cite the relatively low risk of VTE in ambulatory cancer patients and the low absolute reduction in VTE risk with prophylaxis in recommending against routine prophylaxis in ambulatory patients with cancer receiving chemotherapy, with the exception of those with other risk factors, specifically previous VTE, immobilization and concurrent treatment with hormonal therapy, angiogenesis inhibitor therapy, thalidomide and/or lenalidomide [54, 55]. In fact, the low absolute baseline risk of VTE among patients in the PROTECHT trial and the corresponding low absolute reduction in VTE incidence with semuloparin prophylaxis was cited as the primary justification by the U.S. Food and Drug Administration (FDA) for voting against the approval of semuloparin for VTE prophylaxis in this setting. However, as demonstrated above, the baseline risk of VTE among patients with bladder cancer receiving either neoadjuvant or induction chemotherapy is significantly higher than that in the placebo groups of the SAVE-ONCO and PROTECHT trials, such that the absolute risk reduction conferred by VTE prophylaxis in these settings would also be expected to be significantly greater. Of note, an ongoing randomized trial comparing the oral direct factor Xa inhibitor rivaroxaban to placebo for VTE prophylaxis among patients receiving systemic chemotherapy (the CASSINI trial, NCT02555878), is enrolling only patients who are deemed at high risk of VTE as defined by a Khorrana score of two or greater [56]. A randomized trial of pharmacologic VTE prophylaxis among patients with bladder cancer undergoing NCT is currently lacking and is needed to determine the true absolute benefit of VTE prophylaxis in this unique patient population.

Given that patients with bladder cancer are also at increased risk of ATE, it is likewise important to address modifiable risk factors for atherosclerosis such as hypertension, dyslipidemia and diabetes mellitus prior to initiation of chemotherapy. Institution of primary prevention strategies, such as administration of aspirin and statins as well as smoking cessation, should also be considered. A phase one study assessing combined aspirin and simvastatin in

patients with cancer undergoing chemotherapy is currently enrolling patients (NCT02285738). Patients starting chemotherapy should also be educated about signs and symptoms of acute coronary syndromes and stroke.

## CONCLUSIONS AND TAKE-HOME MESSAGES

Surgery and chemotherapy both contribute to the increased risk of TE in patients with bladder cancer. The development of TE is associated with a worse prognosis, partially because it may reflect a more aggressive disease biology. While accumulating evidence supports extended pharmacologic prophylaxis in patients undergoing RC, the risk-benefit ratio for prophylaxis among ambulatory patients undergoing chemotherapy remains uncertain, such that prospective trials addressing this issue are needed.

## FUNDING SOURCES

None

## CONFLICTS OF INTEREST

None

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