Review Article

Extended Venous Thromboembolism Prophylaxis after Radical Cystectomy: A Call for Adherence to Current Guidelines

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Abbreviations and Acronyms

AUA = American Urological Association
CrCl = creatinine clearance
DVT = deep venous thrombosis
EAU = European Association of Urology
ERAS® = enhanced recovery after surgery
GFR = glomerular filtration rate
LMWH = low-molecular-weight heparin
NAC = neoadjuvant chemotherapy
PE = pulmonary embolism
PLND = pelvic lymph node dissection
RC = radical cystectomy
RCT = randomized controlled trial
RP = radical prostatectomy
VTE = venous thromboembolism

Purpose: Radical cystectomy is inherently associated with morbidity. We assess the timing and incidence of venous thromboembolism, review current guideline recommendations and provide evidence for considering extended venous thromboembolism prophylaxis in all patients undergoing radical cystectomy.

Materials and Methods: We searched PubMed® for available literature on radical cystectomy and venous thromboembolism, focusing on incidence and timing, evidence supporting extended venous thromboembolism prophylaxis in patients undergoing radical cystectomy or abdominal oncologic surgery, current guideline recommendations, safety considerations and direct oral anticoagulants. Search terms included "radical cystectomy," "venous thromboembolism," "prophylaxis," and "extended oral anticoagulants" and "direct oral anticoagulants" alone and in combination. Relevant articles were reviewed, including original research, reviews and clinical guidelines. References from review articles and guidelines were also assessed to develop a narrative review.

Results: The incidence of symptomatic venous thromboembolism in short-term followup after radical cystectomy is 3% to 11.6%, of which more than 50% of cases will occur after hospital discharge. Meta-analyses of clinical trials in patients undergoing major abdominal oncologic operations suggest a decreased risk of venous thromboembolisms for patients receiving extended (4 weeks) venous thromboembolism prophylaxis. Extended prophylaxis should be considered in all radical cystectomy cases. Although the relative risk of bleeding also increases, the overall net benefit of extended prophylaxis clearly favors use for at least 28 days postoperatively. Extrarenal eliminated prophylaxis agents are preferred given the risk of renal insufficiency in radical cystectomy cases, with newer oral anticoagulants providing an alternative route of administration.

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Conclusions: Patients undergoing radical cystectomy are at high risk for venous thromboembolism after hospital discharge. There is strong evidence that extended prophylaxis significantly decreases the risk of venous thromboembolism in oncologic surgery cases. Use of extended prophylaxis after radical cystectomy has been poorly adopted, emphasizing the need for better adherence to current urology procedure specific guidelines as extended prophylaxis for radical cystectomy is the standard of care. Specific and rare circumstances may require case by case assessment.

Key Words: urinary bladder neoplasms; cystectomy; venous thromboembolism; heparin, low-molecular-weight

RADICAL cystectomy remains the gold standard treatment for patients with muscle invasive bladder cancer, although the procedure has inherent risks of postoperative morbidity, including bowel anastomotic leak, wound infection, pneumonia and venous thromboembolism. Previous studies have identified major risk factors for venous thromboembolism, including recent surgery, active malignancy and treatment with chemotherapy.[1] Clinical venous thromboembolism in oncology patients is associated with a 2.2-fold increase in mortality compared to patients without venous thromboembolism.[2] Furthermore, prospective studies have revealed venous thromboembolism as one of the most common causes of death among oncology patients (448 per 100,000), second only to disease progression.[3]

Given the high risk of VTE for patients undergoing RC,[4–12] and lack of adherence to current guidelines that suggest extended prophylaxis for high risk patients,[13–19] there appear to be barriers to guideline adoption and/or knowledge translation. A growing body of literature in other surgical disciplines supports use of extended VTE prophylaxis following major abdominal oncologic surgery.[14,20–22] Current evidence specific to the urological literature supports a similar practice, specifically for RC cases.[4,5,12,23] A recently published systematic review and meta-analysis for procedure specific risks of thrombosis and bleeding in uro-oncologic operations[4] and the newly published EAU thromboprophylaxis guideline[13] provide additional evidence supporting extended prophylaxis. We review the timing and incidence of VTE following RC, the current guidelines in this at risk population and the role of extended VTE prophylaxis in these patients. We also review safety considerations and the new direct oral anticoagulants.

MATERIALS AND METHODS

We searched PubMed for available literature on RC and VTE, focusing on incidence and timing, evidence supporting extended VTE prophylaxis (among RC and abdominal oncologic surgery cases), current guideline recommendations, safety considerations and direct oral anticoagulants (specifically in the orthopedic literature). Search terms included "radical cystectomy," "venous thromboembolism," "prophylaxis," and "extended oral anticoagulants" and "direct oral anticoagulants" alone and in combination. References from review articles and guidelines were also assessed to develop a narrative review. Specifically we conducted an extensive systematic review of thromboprophylaxis for uro-oncologic procedures,[4] and the EAU thromboprophylaxis guideline[13] and accompanying references to provide a narrative for using extended VTE prophylaxis for patients undergoing RC.

INCIDENCE AND TIMING OF VTE IN RC CASES

Current reports suggest that the incidence of symptomatic VTE in short-term followup after RC is 3% to 11.6%.[4–12] A systematic review and meta-analysis further stratified patients by surgical approach, comparing VTE risk for patients undergoing open vs robotic RC.[4] Risk of VTE was stratified according to patient risk factors, which were categorized as low (no risk factors), intermediate (age 75 years or older, body mass index 35 kg/m^2 or greater, VTE in a first-degree relative) or high (prior VTE or any combination of 2 or more risk factors).[24] Among 9 studies (3,036 patients) with appropriate criteria for individuals undergoing open RC the risk of VTE was 2.9% in low risk, 5.8% in intermediate risk and 11.6% in high risk patients.[4] Of the 5 studies (1,320 patients) with appropriate criteria for individuals undergoing robotic RC the corresponding VTE risk was 2.6%, 5.2% and 10.3%. Importantly the risk of bleeding necessitating reoperation was only 0.3% regardless of operative approach.

Institutional and population level studies have also assessed incidence of VTE for patients undergoing RC. In a retrospective analysis 2,316 patients underwent RC from 1971 to 2012 at the University of Southern California, including 109 patients (4.7%) suffering from clinically significant VTEs (DVT in 2.1%, PE in 2.6%).[7] Alberts et al identified 27,455 patients in NSQIP® (National Surgical Quality Improvement Program®) who underwent major uro-oncologic surgery between 2005 and 2012.[6] VTE was more likely to develop in patients undergoing RC (113 of 2,065 patients, 5.5%) within