Editorial

Decreasing incidence of venous thromboembolic events after radical cystectomy: are we finally improving?

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Radical cystectomy (RC) is associated with significant postoperative morbidity, including venous thromboembolism (VTE). Current reports suggest that the incidence of symptomatic VTE after RC ranges widely, from 2.6% to 11.6% (1-4), based on patient characteristics and variation between studies. However, current data suggests that this risk is essentially unchanged regardless of surgical approach: the VTE risk for open RC has been estimated in a prior review to be 2.9%, 5.8%, and 11.6% for low, intermediate and high-risk patients, respectively; for robotic RC the corresponding VTE risk was 2.6%, 5.2%, and 10.3% (1). As such, there has been several reports advocating for increased awareness of this potentially modifiable complication and for adherence to guidelines for extended VTE prophylaxis for patients undergoing high-risk abdominal oncologic procedures, such as RC (5).

In a recently published article, Lyon *et al.* (6) critically assessed a contemporary population-based cohort of RC patients treated between 2011 and 2016, noting for the first time a decreasing incidence of VTE over time. Using data from the American College of Surgeons National Surgical Improvement Program (NSQIP) database, among 8,241 patients who underwent RC, Lyon *et al.* noted a significant decrease in VTE incidence rates from 5.1% in 2011 to 2.8% in 2016 (Cochran-Armitage test for trend, P=0.001). Furthermore, this trend held when VTE events were sub-stratified into deep vein thromboses (DVT, 3.6–1.9%, P=0.008) and pulmonary embolism (PE, 3.0–1.3%, P=0.005).

Multivariable logistic regression analysis demonstrated that body mass index (BMI) ≥35 kg/m^2 (OR 1.64, 95% CI, 1.15–2.35), preoperative congestive heart failure (OR 3.11, 95% CI, 1.37–7.04), increased operative time (OR 1.71, 95% CI, 1.23–2.37), continent urinary diversion (OR 1.47, 95% CI, 1.10–1.97), receipt of a perioperative blood transfusion (OR 1.32, 95% CI, 1.06–1.65), and postoperative infection (OR 1.74, 95% CI, 1.33–2.37) or sepsis (OR 2.37, 95% CI, 1.77–3.16) were associated with an increased likelihood of post-operative VTE. Furthermore, the authors report that nearly half of VTE events occurred following hospital discharge, consistent with prior literature (5). The authors appropriately noted several limitations of the NSQIP database, including poor reporting of neoadjuvant chemotherapy [which increases risk of VTE (5)], preoperative VTE incidence [which may be as high as 14% for subclinical VTE (7)], and receipt of VTE prophylaxis.

These data are notable as, to our knowledge, this is the first population-level analysis to suggest a decreasing incidence of VTE over time for patients undergoing RC. A previous study using the NSQIP database assessing VTE incidence among all thoraco-abdominopelvic oncologic surgeries, including RC, from 1999 to 2009 found increasing rates of VTE over time (8), paralleling other

studies over the same time frame that looked at overall VTE rates in the United States (9,10). The discrepancy between these studies and the work of Lyon *et al.* may be explained, optimistically, as a true change in outcome which simply did not begin occurring until after these prior analyses had ceased inclusion or, less optimistically, as a form of detection bias (with prior increases simply reflecting changing scrutiny for these complications) or ecological fallacy (due to changes in the captured population). As mentioned by Lyon *et al.* (6), there has been increasing numbers of RC cases included in the NSQIP database (2,065 cases between 2005 and 2012, and 8,241 cases between 2011 and 2016), suggesting improved participation among registered institutions. When comparing older RC VTE studies using NSQIP to the current study, patient demographics and comorbidities appear to be comparable, suggesting that the observed improvement in VTE incidence rates in more recent years (6) may represent true improvement.

While improvement, in any surgical outcome, is to be welcomed, a better understanding of the factors underpinning the changes in VTE incidence offers the opportunity to potentiate such improvements. Unfortunately, due to the limitations in data abstracted in the NSQIP database, it is not possible to assess the utilization or type of VTE prophylaxis patients received. However, there are two protocols for RC patients that may explain a decrease in VTE incidence rates. First, the Enhanced Recovery After Surgery (ERAS) protocol recommends patients undergoing RC to receive VTE chemoprophylaxis for 4 weeks postoperatively, beginning one day preoperatively (11). While there is evidence to suggest that ERAS has utility for decreasing hospital length of stay and associated healthcare costs without increasing morbidity, there is limited evidence suggesting that ERAS protocols decrease VTE rates (12-16). A limitation of ERAS studies is the inconsistent reporting of VTE rates, considering that evaluation of VTE event rates were not these study's primary or secondary outcome. Clinically, we believe that implementation of ERAS protocols should assist with decreasing VTE incidence rates, considering that extended VTE prophylaxis is included in the protocol, and that a main feature of ERAS is early mobility and return to preoperative function, both of which should contribute to VTE prevention. Since the ERAS protocol became widely accepted during the study period of the Lyon *et al.* report, conceivably this may at least partially explain a drop in VTE rates. Second, the European Association of Urology (EAU) Guidelines recommend 4 weeks of postoperative VTE prophylaxis for RC patients (17), and similar recommendations are made by the American College of Chest Physicians for high risk postoperative patients, including RC (18). Additionally, there have been several RCTs demonstrating a significant risk reduction in patients who receive extended VTE chemoprophylaxis compared to short term prophylaxis following major oncologic abdominopelvic surgery (19-22).

Despite this level-1 evidence among non-RC patients advocating for extended VTE chemoprophylaxis, as well as guideline recommendations (1) and institutional studies (2) demonstrating benefit, there has been resistance to adopting these clinical measures (5). A 2013 survey of American Urologic Association (AUA) members showed only 67.9% of responders endorsed frequently or always using VTE prophylaxis (of any duration) in their patients undergoing RC (23). In that survey, factors associated with more consistent use of VTE prophylaxis included younger age, self-reported sub-specialization in either oncology or laparoscopic/robotics, and awareness of the AUA Best Practice Statement on VTE prophylaxis. Interestingly, this Best Practice Statement from 2009 does not specifically recommend a time-frame or duration of chemoprophylaxis, but does note that RC is one of the most high-risk routinely performed surgery by urologists and should strongly consider multiple methods of VTE prophylaxis (24).

While it is reassuring for urologic oncologists that rates of VTE following RC appear to be falling, there is much work left to do. The present data do not allow us to assess the role of VTE prophylaxis in these changes and prior work has shown that adherence in quite low. As has been consistently reported, more than half of patients experiencing a VTE event do so after discharge from the hospital. Previous work has further suggested that the cumulative incidence of VTE may continue to rise for months following RC (25). Thus, extended thromboprophylaxis is likely warranted for nearly all patients undergoing RC. Further studies exploring barriers to such care are likely to assist in future declines in the rates of VTE.

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Footnote

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to declare.

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