REVIEW PAPER

UROLOGICAL ONCOLOGY

Current thromboprophylaxis in urological cancer patients during COVID-19 pandemic

Adam Ostrowski[1], Piotr Skrudlik[2], Filip Kowalski[1], Paweł Lipowski[1], Magdalena Ostrowska[1], Przemysław Adamczyk[3], Jan Adamowicz[1], Tomasz Drewa[1], Kajetan Juszczak[1,4]

[1]*Department of Urology and Andrology, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Poland*
[2]*Department of Urology, NEO Hospital, Cracow, Poland*
[3]*Department of Urology, Department of General and Oncologic Urology, Nicolaus Copernicus Hospital, Toruń, Poland*
[4]*Department of Urology, Ludwik Rydygier Hospital, Cracow, Poland*

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Corresponding author
Adam Ostrowski
Nicolaus Copernicus University in Toruń
Collegium Medicum in Bydgoszcz
Department of Urology
9 Curie-Skłodowskiej
85-094 Bydgoszcz, Poland
phone +48 607 5772 28
adostro@gmail.com

Introduction Venous thrombosis is a well-known complication of cancer disease, especially in Urology. However, even though proper antithrombotic prophylaxis is crucial in most urological procedures, we have insufficient high-quality studies on this topic. The European Association of Urology (EAU) Guidelines are outdated and lack data on COVID-19 increased risk of thrombosis. This review aimed to summarize data on thromboprophylaxis after radical prostatectomy, cystectomy, and nephrectomy during COVID-19 pandemic.

Material and methods A thorough analysis of the EAU Guidelines of Thromboprophylaxis was performed and compared to PubMed search, considering updated literature on thromboprophylaxis of radical prostatectomy, cystectomy, nephrectomy, as well as COVID-19 influence on venous thrombosis and urological practice.

Results Each patient should be evaluated individually to balance bleeding and venous thromboembolism (VTE) risk. There is still much uncertainty in low and medium-risk patients and all endoscopic procedures, where thromboprophylaxis could be omitted. Patients with COVID infection bear a significantly higher risk of VTE. All patients should be tested for COVID infection prior to a planned surgery during bursts of infections, undependably of vaccination status. Efforts to maintain early cancer diagnosis and treatment during the pandemic should be maintained.

Conclusions The quality of evidence is inadequate, and when deciding on thromboprophylaxis, we need to base it on individual risk, cancer advancement, procedure type, and our own experience.

Key Words: thrombosis ‹› venous thromboembolism ‹› thromboprophylaxis ‹› urologic neoplasms ‹› COVID-19

INTRODUCTION

Venous thrombosis is a well-known complication of cancer disease. Every healthy patient presenting with venous thromboembolism (VTE) episode should be investigated for cancer. Tumor type, the stage, and treatment modality are major risk factors of VTE. Furthermore, age, immobilization, surgeries, and comorbidities will also influence thrombotic complications. Cancer treatment also contributes to increasing cancer patients' thrombotic risk [1]. Even though proper antithrombotic prophylaxis is crucial in most urological procedures, we have insufficient high-quality studies on this topic. The use of thromboprophylaxis in urological procedures is common but not standardized [2]. The current European Association of Urology (EAU) Guidelines on thromboprophylaxis tried to summarize all available data. Although most guidelines are in line with standard practices, some still cause controversies and have only a weak level of evidence. Even though the guidelines were published in 2020, the latest updated references are

from 2018, before the COVID-19 pandemic started [3]. Although in 2020, EAU Guidelines Office Rapid Reaction Group published "An organization-wide collaborative effort to adapt the EAU guidelines recommendations to the COVID-19 era", which addressed many clinical problems, thromboprophylaxis was omitted [4].

This review aimed to summarize the pathophysiology and rationale of using thromboprophylaxis in different urological cancer surgeries. In addition, we highlighted differences between current EAU Guidelines with standard practices. Finally, we also summarized the limited data about the effect of COVID-19 infection on urological practice and venous thrombosis.

MATERIAL AND METHODS

A thorough analysis of the EAU Guidelines of Thromboprophylaxis was performed and compared to PubMed search, considering updated literature on thromboprophylaxis of radical prostatectomy, cystectomy, nephrectomy, as well as COVID-19 influence on venous thrombosis and urological practice.

RESULTS

General considerations about pathophysiology thromboembolism

The hypercoagulable state in cancer is multifactorial. Tumor cells can directly activate the blood clotting cascade and cause thrombosis. They induce pro-coagulant properties and inhibit anticoagulant properties of vascular endothelial cells, platelets, monocytes, and macrophages. Consequently, local and systemic effects of cancer (e.g., stasis induced by prolonged bed rest or vascular invasion by the tumor), together with iatrogenic complications of the treatment of cancer (e.g., the use of central venous catheters and angiopathic chemotherapy), this basic pathophysiology conspires to make cancer perhaps the best example of "acquired thrombophilia" [5]. The hypercoagulability state can be activated by:

1) Tissue factors (TF) expressed by tumor cells, endothelial cells, and monocytes. First, plasma factor VII binds to TF, making FVIIa. FVIIa cut factor X in the next step, changing it into an active form – FXa. In the end, FXa induces thrombin generation, which induces fibrinogen coagulation into fibrin that forms the clot.
2) Tumor cells express TF and cancer pro-coagulant factors. Tumor cells eventually release TF-procoagulant microparticles into the circulation that may later trigger VTE. Moreover, metastasis can release TF on circulating tumor cells, which leads to the adhesion of the cells with fibrin that stops them within the microvasculature. In addition to coagulation activation, it was proven that TF-VIIa using protease-activated receptors PAR2 in tumor cells form TF-VIIa-PAR2 complex that inducing proangiogenic and immune-modulating cytokines, chemokines, and growth factors promoting cancer progression.
3) Tumor cells secrete proinflammatory cytokines responsible for TF expression on endothelial cells such as TNF-α. It can regulate the level of thrombomodulin, the surface receptor for thrombin, at the surface of endothelial cells.
4) Tumor cells, due to interaction with monocytes-macrophages, induce TF expression by these cells.
5) Tumor cells express and release the receptor for protein C. With its receptor and cofactor (protein S), this protein can degrade factors VIa and VIIIa.

Several methods are available for thromboprophylaxis, which are routinely used in the perioperative setting to prevent VTE and its attendant complications [6]. The mechanical devices reduce venous stasis in the lower extremities and release antithrombotic factors from leg muscles. They mainly include graduated compression stockings (GCS), intermittent pneumatic compression (IPC) devices, and venous foot pumps (VFP). Pharmacologic thromboprophylaxis is achieved with subcutaneous low molecular weight heparin (LMWH) or low dose unfractionated heparin (LDUH) [7]. Warfarin and new anticoagulants are not widely used in this recommendation [7].

Individual risk assessment for venous thromboembolism

No matter the performed surgery and specific cancer type, underlying comorbidities play a significant role in VTE risk. As for this publication's need, we present the same risk assessment tool as presented in the EAU guidelines – see Table 1. It offers a quick reference that is easy to use in daily practice [3].

Nevertheless, if possible, the individual risk of VTE should be carefully assessed. Tools such as the Caprini score seem to be more accurate and aid our decision-making [8, 9].

Effect of COVID-19 infection on thromboembolic risk and urological practice

It was quickly discovered that COVID-19 significantly affects the risk of thromboembolic events [10]. The pro-coagulant mechanism may include variables such as increased Factor V [11], lupus anticoagulant [12], reduction of the von Willebrand factor inhibitor [13], amplification of thrombin generation [14], in-

Table 1. *Risk of VTE according to age and comorbidities*

Risk group	Risk factor	Risk of VTE
Low risk	No risk factors	1X
Medium risk	Any one of the following: age 75 years or more; body mass index 35 or more; VTE in 1st degree relative (parent, full sibling, or child)	2X
High risk	Prior VTE Patients with any combination of two or more risk factors	4X

VTE – venous thromboembolism

creased levels of plasminogen activator inhibitor type 1, and hypofibrinolytic state [15]. The mechanism is suggested to be similar to disseminated intravascular coagulation [15].

Doglietto et al. [16] showed that unvaccinated patients with perioperative positive test results for COVID-19 had a highly increased risk of thromboembolic complications compared to patients with negative tests (OR-13.2) [16]. In unvaccinated patients treated due to COVID-19 in the Intensive Care Unit, the thromboembolic incidence is 20–43% [17, 18]. Bearing in mind the risk of an asymptomatic course of COVID-19 infection, the European Society of Clinical Microbiology and Infectious Diseases suggested testing for COVID-19 in all patients before the planned surgeries (within at most 48–72 hours) independent of their vaccination status [19]. Unfortunately, the is no data available on the effect of COVID-19 infection on radical prostatectomy, cystectomy, nor nephrectomy, therefore we can base only on the general surgical experiences [16].

Recently, some authors reported a delay in diagnosing the bladder cancer, resulting in more severe cases [20, 21]. In addition, fewer prostate biopsies were performed, the number of radical prostatectomies dropped by around 20%, and the amount of locally advanced and metastatic prostate cancer disease increased [22, 23]. Most probably, it is caused by the delay of early diagnostics. Advanced cancers may bear a higher risk of thromboembolic complications, especially in the metastatic setting or after neoadjuvant therapy [24, 25].

Prostate cancer

Prostate cancer is one of the most common cancer in men, with over one million patients diagnosed yearly worldwide and accounting for 15% of all cancers diagnosed [26]. The frequency of autopsy-detected prostate cancer (PCa) is roughly the same worldwide. There is relatively less variation in mortality rates worldwide, although rates are generally high in African descent populations, intermediate in the USA, and very low in Asia. Prostate cancer is associated with an increased risk of thromboembolic diseases such as pulmonary embolism (PE) or deep vein thrombosis. Data on the relationship between prostate cancer and thromboembolic diseases are sparse. The overall risk in patients with prostate cancer is four-time higher than in the general population. Several factors play a role in hypercoagulability state pathogenesis. The most potentate risk factors are as follow age and endocrine treatment. Prostate cancer can be treated with curative intention – primarily by operations (radical prostatectomy – open surgery, laparoscopic and robotic-associated), radiotherapy (external beams, brachytherapy, or CyberKnife). When it fails or prostate cancer is too advanced (N+ or M+), only palliative treatment is available (endocrine – sometimes combined with chemotherapy). In the first months, the risk increases in endocrinological and curative treatment, mainly in the first six months, especially for deep-venous thrombosis and pulmonary embolism. For arterial embolism, the trend is not so visible [27]. Following EAU guidelines, the operator should consider pharmacological prophylaxis in almost every open surgery or extended pelvic lymph node dissection (PLND) [3, 28]. There is proven that minimal invasive operation has minimal risk of VTE [3, 28, 29]. In common practice, only in limited situations are pharmacological prophylaxis omitted, and mechanical prophylaxis is introduced in any prostate cancer surgery. A prophylaxis continuation should be continued in high-risk VTE patients after discharge [30].

On the contrary, EAU guidelines recommend against using thromboprophylaxis in case of minimally invasive procedures and robotic and laparoscopic prostatectomies without pelvic lymph node dissections (PLND) in all patients and patients at medium and high risk of VTE in case of performing PNLD. Surprisingly, the same guidelines recommend against using mechanical prophylaxis in laparoscopic and robotic prostatectomies without PNLD in patients at low risk of VTE.

Unfortunately, the mentioned above controversial recommendation strength is weak. We have to bear in mind that there is a considerable risk of selection bias in studies upon which the recommendations were prepared. The majority of data from systematic review and meta-analysis prepared by K Tikkinen et al. were included in studies where the certainty of estimates was low to moderate at best, and the risk of bias was relatively high [31]. Guidelines with strong recommendations mainly refer to open prostatectomies where we should use prophylaxis in ev-

ery patient and all patients with a high risk of VTE undergoing PLND [3].
The vast majority of scientific research concerns patients with hormone- and chemotherapy. [27, 32, 33, 34]. Significant impact on risk factors has the presents of metastases.
The duration of the use of anticoagulant prophylaxis remains an open question. No randomized study has been performed to determine the optimal duration of prophylaxis in almost every urological operation. Moreover – there is no consensus in worldwide statements in urological associations due to the lack of high-level research [35, 36].

Kidney cancer

Renal cell carcinoma represents around 3% of all cancers, with the highest incidence occurring in Western countries [37]. Until recently, there has been an annual increase of about 2% in incidence worldwide in the last two decades. Only in the European Union in 2018, almost 100 thousand new cases of renal cell carcinoma (RCC) and almost 40 thousand kidney cancer-related deaths were recorded [37]. RCC is associated with a high risk of VTE. In localized disease, the risk rate is approximately 1.3%, and it grows to 3.8% in regionally advanced disease during 2-year follow-up after optimal treatment (nephrectomy/tumorectomy) [38]. Tumor thrombus is a unique feature of RCC. Nevertheless, only a few studies have reported its clinical effect on the occurrence of venous thromboembolism. Patients with tumor thrombus had a significantly higher VTE incidence than those without thrombus. It can be associated with formatting thrombus on suturing site suturing vena cava inferior following removing the cloth. In univariable analysis, the major risk factors were age above 60 years, advanced T stage, the presence of tumor thrombus, an increased preoperative platelet count (>400 × 103/μL) and CRP (>0.5 mg/dL) was associated with a significantly increased incidence of VTE when all patients were considered [6]. Additionally, tumor thrombus was independently associated with worse progression-free survival (PFS), but not overall survival in multivariable analysis [6]. Nevertheless, postoperative management is vastly different among urological centers –mainly after hospitalizations. EAU guidelines and most available publications recommend using thromboprophylaxis in such a case [3, 35].
In actual EAU guidelines pros and cons of using thromboprophylaxis in renal surgery are widely different (for pharmacological prophylaxis) – depending on the extent of the procedure and its modality of surgery [nephrectomy/tumorectomy; open/laparo- scopic; with/without inferior vena cave (IVC) thrombus] [3, 30, 39, 40]. Only mechanical prophylaxis is recommended in all options. The majority of recommendations certainty is graded very low, as the quality of evidence is insufficient [3]. The aforementioned guidelines are based on several studies, which are inconsistent with VTE's definitions and bleeding. Furthermore, many of included studies have no control arm [35]. We may only assume that VTE's assessment should be carefully carried out in every patient out of such low-quality studies. We may also assume that laparoscopic and robotic procedures carry a slightly lower VTE risk [35].

Bladder cancer

Bladder cancer (BC) is the seventh most commonly diagnosed cancer in the male population worldwide, while it drops to eleventh when both genders are considered [26]. Approximately three-fourths of patients with BC are diagnosed with non-muscle invasive disease. In younger patients (<40), this fraction is even higher [41]. Patients with TaT1 and carcinoma in situ (CIS) have a high prevalence due to long-term survival in many cases, and a lower risk of cancer-specific mortality (CSM) compared to T2-4 tumors [41, 42]. A patient can be treated radically by endoscopy (pTa-T1), open/laparoscopic/robotic – associated radical cystectomy (RC) (≥T2 NxMx) with adjuvant/neoadjuvant chemotherapy. Patients with advanced (≥pT2) bladder cancer are at high risk of developing venous and arterial thromboembolic events. Radical cystectomy has the highest VTE risk compared with other urological operations. Several studies have noted that radical cystectomy has the highest risk of postoperative VTE among urologic surgeries [43, 44, 45]. PE is an important factor of complications and death after cystectomy [46, 47]. Rishi Naik et al. results revealed that the highest risk group are patients operated in an open and robotic modality of radical cystectomy (2.6–11.6%) [35]. Neoadjuvant chemotherapy (NAC) also increases the risk of VTE events [48, 49]. There is an increased risk of deep venous thrombosis in patients with NAC, mostly preoperative (but the postoperative risk is the same) [50]. There is no data on VTE risk when using immunotherapy due to bladder cancer. It is suggested that immune checkpoint inhibitors carry a similar VTE risk to other systematic therapies [51]. The incidence of symptomatic VTE in short-term follow-up after RC is 3% to 11.6%. More than half of cases will occur after hospital discharge [49, 52]. Patients with thromboprophylaxis experience a significantly lower DVT rate (5.06%), assessed as 90 days postoperatively. There are no significant differences between using thromboprophylaxis and not doing so in the overall complication rate (54.4% vs 68.6%),

the hemorrhagic complication rate (3.7% vs 2.0%), and the readmission rate (21.5% vs 29.4%).

VTE prophylaxis should be routinely used in all patients undergoing RC. Even though the relative risk of bleeding also increases, extended prophylaxis's overall net benefit favors use for at least 28 days postoperatively [53].

EAU guidelines recommend mechanical and pharmacological prophylaxis, both in robotic and open RC. Only pharmacological prophylaxis in open surgery has a strong recommendation [3].

Another critical matter is bleeding complications during and after radical cystectomy. For the reduction of peri- and postoperative blood loss and the need for blood transfusion in adult patients undergoing radical cystectomy, there is a possibility to administer tranexamic acid – loading dose of 10 mg/kg tranexamic acid, followed by infusion of 5 mg/kg/h for the duration of surgery. There is an ongoing randomized controlled trial of this procedure to assess the median reduction counts of blood units needed to transfer and ensure this procedure's safety [54].

CONCLUSIONS

Each patient should be evaluated individually to balance bleeding and VTE risk. There is no doubt in using thromboprophylaxis in high risk of VTE patients, advanced or metastatic tumors, and open surgeries. There is still much uncertainty in low and medium-risk patients and all endoscopic procedures. All patients should be tested for COVID-19 infection prior to a planned surgery during bursts of infections, undependably of vaccination status. Efforts to maintain early cancer diagnosis and treatment during pandemic should be maintained, as advanced tumors have the worst prognosis and bear a higher risk of thromboembolic complications. The quality of evidence is inadequate, and when deciding on thromboprophylaxis, we need to base it on individual risk, cancer advancement, procedure type, and own experience.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

References

1. Mirshahi S, Pocard LL, Mirshahi M, Soria J. Pathogenesis and Diagnosis of Venous Hypercoagulable States in Cancer. J Hematol Thrombo Dis. 2015; 3: 3-4.
2. Violette PD, Vernooij RWM, Aoki Y, et al. An International Survey on the Use of Thromboprophylaxis in Urological Surgery. Eur Urol Focus. 2021; 7: 653-658.
3. Tikkinen (Chair) RC, Gould MK, Naspro R, et al. Thromboprophylaxis. EAU Guidelines Edn presented at the EAU Annual Congress Amsterdam, 2020. ISBN 978-94-92671-07-3
4. Ribal MJ, Cornford P, Briganti A, et al. European Association of Urology Guidelines Office Rapid Reaction Group: An Organisation-wide Collaborative Effort to Adapt the European Association of Urology Guidelines Recommendations to the Coronavirus Disease 2019 Era. Eur Urol. 2020; 78: 21-28.
5. Falanga A, Rickles FR. Pathophysiology of the thrombophilic state in the cancer patient. Seminars in thrombosis and hemostasis. Semin Thromb Hemost. 1999; 25: 173-182.
6. Park H, Jeong CW, Yuk H, et al. Influence of Tumor Thrombus on Occurrence of Distant Venous Thromboembolism and Survival in Patients With Renal Cell Carcinoma After Surgery. Clin Appl Thromb Hemost. 2019; 25: 1076029618823288.
7. Hariharan U, Venous SB. Thromboembolism and Robotic Surgery: Need for Prophylaxis and Review of Literature. J Hematol Thrombo Dis. 2015; 3: 1-5.
8. Bartlett MA, Mauck KF, Stephenson CR, Ganesh R, Daniels PR. Perioperative Venous Thromboembolism Prophylaxis. Mayo Clin Proc. 2020; 95: 2775-2798.
9. Cronin M, Dengler N, Krauss ES, et al. Completion of the Updated Caprini Risk Assessment Model (2013 Version). Clin Appl Thromb Hemost. 2019; 25: 1076029619838052.
10. Thachil J, Agarwal S. Understanding the COVID-19 coagulopathy spectrum. Anaesthesia. 2020; 75: 1432-1436.
11. Stefely JA, Christensen BB, Gogakos T, et al. Marked factor V activity elevation in severe COVID-19 is associated with venous thromboembolism. Am J Hematol. 2020; 95: 1522-1530.
12. Bowles L, Platton S, Yartey N, et al. Lupus Anticoagulant and Abnormal Coagulation Tests in Patients with Covid-19. N Engl J Med. 2020; 383: 288-290.
13. Tiscia GL, Favuzzi G, De Laurenzo A, et al. Reduction of ADAMTS13 Levels Predicts Mortality in SARS-CoV-2 Patients. TH Open. 2020; 4: e203-e206.
14. Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. J Thromb Haemost. 2020; 18: 1747-1751.
15. Nougier C, Benoit R, Simon M, et al. Hypofibrinolytic state and high thrombin generation may play a major role in SARS-COV2 associated thrombosis. J Thromb Haemost. 2020; 18: 2215-2219.
16. Doglietto F, Vezzoli M, Gheza F, et al. Factors Associated With Surgical Mortality and Complications Among Patients With and Without Coronavirus Disease 2019 (COVID-19) in Italy. JAMA Surg. 2020; 155: 691-702.
17. Klok FA, Kruip M, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020; 191: 145-147.
18. Cryer MJ, Farhan S, Kaufmann CC, et al. Prothrombotic Milieu, Thrombotic Events and Prophylactic Anticoagulation in Hospitalized COVID-19 Positive Patients: A Review. Clin Appl Thromb Hemost. 2022; 28: 10760296221074353.

19. Carrara E, Ong DSY, Hussein K, et al. ESCMID guidelines on testing for SARS-CoV-2 in asymptomatic individuals to prevent transmission in the healthcare setting. Clin Microbiol Infect. 2022; 28: 672-680.

20. Bersanelli M, Buti S, Rizzo M, et al. GU-CA-COVID: a clinical audit among Italian genitourinary oncologists during the first COVID-19 outbreak. Ther Adv Urol. 2021; 13: 17562872211054302.

21. Oderda M, Soria F, Rosi F, et al. COVID-19 pandemic impact on uro-oncological disease outcomes at an Italian tertiary referral center. World J Urol. 2022; 40: 263-269.

22. Pepe P, Pepe L, Pennisi M, Fraggetta F. Prostate Cancer Diagnosis and Management During One Year of the COVID-19 Pandemic. Anticancer Res. 2021; 41: 3127-3130.

23. Zattoni F, Marra G, Kretschmer A, et al. Has the COVID-19 outbreak changed the way we are treating prostate cancer? An EAU- YAU Prostate Cancer Working Group multi-institutional study. Cent European J Urol. 2021; 74: 362-365.

24. Di Nisio M, Candeloro M, Rutjes AWS, Porreca E. Venous thromboembolism in cancer patients receiving neoadjuvant chemotherapy: a systematic review and meta-analysis. J Thromb Haemost. 2018; 16: 1336-1346.

25. Ramos JD, Wingate JT, Gulati R, et al. Venous Thromboembolism Risk in Patients With Locoregional Urothelial Tract Tumors. Clin Genitourin Cancer. 2017 doi: 10.1016/j.clgc.2017.08.001 [Online ahead of print].

26. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015; 136: E359-E386.

27. Van Hemelrijck M, Adolfsson J, Garmo H, et al. Risk of thromboembolic diseases in men with prostate cancer: results from the population-based PCBaSe Sweden. Lancet Oncol. 2010; 11: 450-458.

28. Weinberg A, Wright J, Deibert C, et al. Nationwide practice patterns for the use of venous thromboembolism prophylaxis among men undergoing radical prostatectomy. World J Urol. 2014; 32: 1313-1321.

29. Krimphove MJ, Reese S, Chen X, et al. Minimally invasive cancer surgery is associated with a lower risk of venous thromboembolic events. J Surg Oncol. 2020; 121: 578-583.

30. Alberts BD, Woldu SL, Weinberg AC, Danzig MR, Korets R, Badani KK. Venous thromboembolism after major urologic oncology surgery: a focus on the incidence and timing of thromboembolic events after 27,455 operations. Urology. 2014; 84: 799-806.

31. Tikkinen KAO, Craigie S, Agarwal A, et al. Procedure-specific Risks of Thrombosis and Bleeding in Urological Cancer Surgery: Systematic Review and Meta-analysis. Eur Urol. 2018; 73: 242-351.

32. Dubinsky S, Thawer A, McLeod AG, McFarlane TRJ, Emmenegger U. Management of anticoagulation in patients with metastatic castration-resistant prostate cancer receiving abiraterone + prednisone. Support Care Cancer. 2019; 27: 3209-3217.

33. Guo Z, Huang Y, Gong L, et al. Association of androgen deprivation therapy with thromboembolic events in patients with prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis. 2018; 21: 451-460.

34. Klil-Drori AJ, Yin H, Tagalakis V, Aprikian A, Azoulay L. Androgen Deprivation Therapy for Prostate Cancer and the Risk of Venous Thromboembolism. Eur Urol. 2016; 70: 56-61.

35. Naik R, Mandal I, Hampson A, et al. The role of extended venous thromboembolism prophylaxis for major urological cancer operations. BJU Int. 2019; 124: 935-944.

36. Violette PD, Cartwright R, Briel M, Tikkinen KA, Guyatt GH. Guideline of guidelines: thromboprophylaxis for urological surgery. BJU Int. 2016; 118: 351-358.

37. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer. 2018; 103: 356-387.

38. Chew HK, Wun T, Harvey D, Zhou H, White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch Intern Med. 2006; 166: 458-464.

39. Lund L, Nisen H, Jarvinen P, et al. Use of venous-thrombotic-embolic prophylaxis in patients undergoing surgery for renal tumors: a questionnaire survey in the Nordic countries (The NORENCA-2 study). Res Rep Uro. 2018; 10: 181-187.

40. Jordan BJ, Matulewicz RS, Trihn B, Kundu S. Venous thromboembolism after nephrectomy: incidence, timing and associated risk factors from a national multi-institutional database. World J Urol. 2017; 35: 1713-1719.

41. Comperat E, Larre S, Roupret M, et al. Clinicopathological characteristics of urothelial bladder cancer in patients less than 40 years old. Virchows Arch. 2015; 466: 589-594.

42. Burger M, Catto JW, Dalbagni G, et al. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol. 2013; 63: 234-241.

43. Clement C, Rossi P, Aissi K, et al. Incidence, risk profile and morphological pattern of lower extremity venous thromboembolism after urological cancer surgery. J Urol. 2011; 186: 2293-2297.

44. Hammond J, Kozma C, Hart JC, et al. Rates of venous thromboembolism among patients with major surgery for cancer. Ann Surg Oncol. 2011; 18: 3240-3247.

45. De Martino RR, Goodney PP, Spangler EL Variation in thromboembolic complications among patients undergoing commonly performed cancer operations. J Vasc Surg. 2012; 55: 1035-1040 e4.

46. Scarpa RM, Carrieri G, Gussoni G, et al. Clinically overt venous thromboembolism after urologic cancer surgery: results from the @RISTOS Study. Eur Urol. 2007; 51: 130-135.

47. Quek ML, Stein JP, Daneshmand S, et al. A critical analysis of perioperative mortality from radical cystectomy. J Urol. 2006; 175 (3 Pt 1): 886-889.

48. Ottosson K, Pelander S, Johansson M, Huge Y, Aljabery F, Sherif A. The increased risk for thromboembolism pre-cystectomy in patients undergoing neoadjuvant chemotherapy for muscle-invasive urinary bladder cancer is mainly due to central venous access: a multicenter evaluation. Int Urol Nephrol. 2020; 52: 661-669.

49. Brennan K, Karim S, Doiron RC, Siemens DR, Booth CM. Venous Thromboembolism and Peri-Operative

Chemotherapy for Muscle-Invasive Bladder Cancer: A Population-based Study. Bladder Vancer. 2018; 4: 419-428.

50. Schomburg JL, Krishna S, Cotter KJ, Soubra A, Rao A, Konety BR. Preoperative Incidence of Deep Venous Thrombosis in Patients With Bladder Cancer Undergoing Radical Cystectomy. Urology. 2018; 116: 120-124.

51. Gutierrez-Sainz L, Martinez-Marin V, Vinal D, et al. Incidence of venous thromboembolic events in cancer patients receiving immunotherapy: a single-institution experience. Clin Transl Oncol. 2021; 23: 1245-1252.

52. Klaassen Z, Arora K, Goldberg H, et al. Extended Venous Thromboembolism Prophylaxis after Radical Cystectomy: A Call for Adherence to Current Guidelines. J Urol. 2018; 199: 906-914.

53. Pariser JJ, Pearce SM, Anderson BB, et al. Extended Duration Enoxaparin Decreases the Rate of Venous Thromboembolic Events after Radical Cystectomy Compared to Inpatient Only Subcutaneous Heparin. J Urol. 2017; 197: 302-307.

54. Breau RH, Lavallee LT, Cnossen S, et al. Tranexamic Acid versus Placebo to Prevent Blood Transfusion during Radical Cystectomy for Bladder Cancer (TACT): Study Protocol for a Randomized Controlled Trial. Trials. 2018; 19: 261.