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EDITORIAL COMMENT

When Clot Is Tumor

A Roadmap to Anticoagulation in Renal Cell Carcinoma With Tumor Thrombus*

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The role of anticoagulation in preventing thromboembolic events is understudied in renal cell carcinoma (RCC). In view of the oncologic literature, other cancer types, such as metastatic adenocarcinoma of cholangial or pancreatic origin, are models where the role of anticoagulation has been studied more extensively.[1] In pancreatic cancer, which has a 4-fold increased risk of venous thromboembolic events (VTEs) compared with other cancers, low molecular weight heparin (LMWH) has been shown to be superior to warfarin in reducing recurrent VTE. Direct oral anticoagulants (DOACs) have also been assessed and are approved for thromboembolic events, but the efficacy is less than with LMWH. However, some critical differences exist between RCC and pancreatic adenocarcinoma: RCCs are unique in that they form large tumor thrombi. RCC is treated with immunomodulatory therapy and/or antiangiogenic therapy rather than chemotherapy.

In this issue of *JACC: CardioOncology*, Kaptein et al[2] performed a retrospective analysis of 647 patients with RCC at the Leiden University Medical Center in the Netherlands from 2010 to 2019 and found 86 patients at diagnosis with tumor thrombus characterized as involving the renal vein, inferior vena cava (IVC), or IVC extending above the diaphragm. Fifty-two patients had disease extending into the IVC or higher. The investigators defined the incidence of venous thrombosis, arterial thrombosis, bleeding, and death from these events. Seventeen of the 86 patients developed a venous thrombotic event, and 11 of 86 experienced a major bleeding event. Some patients receiving anticoagulation still developed thrombotic events and at a cost of bleeding. VTEs occurred in patients with tumor thrombi extending into the IVC or higher; this may be reflective of tumor aggressiveness rather than the actual cranial extent of the thrombus. The investigators should be recognized for characterizing this large group of patients. This study elucidated the natural history of tumor thrombi in RCC, including risk factors, incidence, rates of recurrence, and thrombus extension. Data on outcomes in thrombus type and location, as well as mortality between treatment groups, are important to inform clinical surveillance and therapy selection. Although there was attrition to the patient population follow-up, retrospective data can be informative because randomized studies of anticoagulation are challenging to conduct in this setting.

Across cancer types, guidance on anticoagulation for tumor thrombus is sparse and does not address anticoagulant type or dosage. In 153 patients with tumor thrombus (most commonly RCC or hepatocellular carcinoma), proportionally more patients on anticoagulation developed VTE (61%) vs not (39%).[3] In a series focused on advanced pancreatic cancer patients, anticoagulation use was potentially associated with improved ascites and decreased thrombus progression, with only a 7% incidence of minor bleeding.[4] These studies differed from that of Kaptein et al[2] by tumor type and outcome measures, and likely owing to sample size constraints, did not further characterize anticoagulation.

The distinction between prophylactic and therapeutic dose anticoagulation is important, as

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dose increases reduce VTE incidence, but at the cost of increased bleeding. Index VTE events in patients with active cancer were estimated at 5.8/100 person-years,[5] which is substantially lower than the 22% cumulative incidence over 2 years in this study, in which 30% received anticoagulation. Although more data are needed, therapeutic anticoagulation in select high-risk patients may be reasonable. Notably, the majority in this study were prescribed LMWH, which was the anticoagulant agent of choice over warfarin and unfractionated heparin. Recent large randomized controlled trials comparing DOACs to LMWH have favored DOACs in reducing recurrent VTEs, with a pooled meta-analysis of 4 trials reporting recurrent VTE rates at 5.2% for DOACs and 8.2% for LMWH, at the expense of more frequent significant bleeding.[6,7] Similar data support DOAC use in thromboprophylaxis. DOACs have advantages in ease of administration and improved adherence, and apixaban can be dosed in end-stage renal disease. LMWH, however, has fewer drug-drug interactions and can be dose-adjusted with breakthrough VTEs. The importance of careful selection of anticoagulation is highlighted by this study's numerically higher mortality rates (although not statistically significant) in patients with tumor thrombi on anticoagulation vs those without. Anticoagulation may have been selected in those with greater risk for mortality, although reduced VTE incidence does not necessarily translate to decreased mortality. Pending further data, clinicians may opt to select anticoagulation in high-risk patients where functional or cardiopulmonary concerns favor VTE prevention over bleeding risk.

As Kaptein et al[2] point out, anticoagulation in their population was limited to therapeutic dosage and mostly consisted of LMWH. However, the tendency in clinical practice is toward increasing use of DOACs in cancer patients, thus affecting the generalizability of the reported findings. Analogous studies surveying DOAC usage in tumor thrombi and prophylactic dosing may help provide data to inform the balance between thrombosis and bleeding in clinical practice. Additional limitations include the potential risk of unmeasured confounding, and the need to test the efficacy of anticoagulation on other endpoints, such as metastatic spread and symptomatic burden.

Tumor invasion of the vasculature and associated higher tumor grade increase the risk of metastasis in this population. Extension of tumor thrombi also increases surgical complications, although it is uncertain whether level is associated with prognosis.[8] Preclinical data point to coagulation factors as generators of tumor progression and metastasis, which has been variably borne out in clinical studies.[9,10] Angiogenesis and metastasis could feasibly be stunted by anticoagulation. As illustrated by Kar et al,[4] tumor thrombi also cause downstream vascular dysfunction. In the case of IVC thrombi, lower extremity edema, venous stasis ulcers, and deconditioning are potential consequences impacting quality of life and even survival. Further studies may address the benefit of anticoagulation on these important outcomes. Kaptein et al[2] further found that removal of tumor thrombus did not lower VTE incidence. Radical nephrectomy and thrombectomy is the optimal approach in most cases, however the procedure raises VTE risk in the postoperative period.[11] Other factors that heighten VTE risk, such as IVC luminal disruption from tumor thrombus[12] and residual tumor thrombus,[13] may remain, potentially contributing to the equivalent clot incidence after thrombectomy. These and other questions raised by this important study will help illuminate a common grey area in a highly morbid setting.

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REFERENCES

1. Moffat GT, Epstein A, O'Reilly E. Pancreatic cancer–a disease in need: optimizing and integrating supportive care. *Cancer*. 2019;125(22):3927–3935.

2. Kaptein FHJ, van der Hulle T, Braken SJE, et al. Prevalence, treatment, and prognosis of tumor thrombi in renal cell carcinoma. *J Am Coll Cardiol CardioOnc*. 2022;4(4):522–531.

3. Marcoux C, Al Ghamdi S, Manos D, Keating M-M, Shivakumar SP. Natural history of tumor thrombus: a single-centre retrospective study. *Blood*. 2019;134:430.

4. Kar SP, Bhosale P, Overman MJ, et al. Role of anticoagulation (AC) in patients with advanced pancreatic cancer (APC) with splanchnic venous thrombosis (SVT). *J Clin Oncol*. 2011;29(15 suppl). e14622-e14622.

5. Cohen AT, Katholing A, Rietbrock S, Bamber L, Martinez C. Epidemiology of first and recurrent venous thromboembolism in patients with active cancer. A population-based cohort study. *Thromb Haemost*. 2017;117(1):57–65. https://doi.org/10.1160/TH15-08-0686

6. Brea EJ, Tiu BC, Connors JM. A comprehensive review of DOACs for cancer associated VTE prophylaxis or treatment. *Postgrad Med*. 2021;133(suppl 1):71–79. https://doi.org/10.1080/00325481.2021.1955542

7. Mosarla RC, Vaduganathan M, Qamar A, Moslehi J, Piazza G, Giugliano RP. Anticoagulation strategies in patients with cancer: JACC review topic of the week. *J Am Coll Cardiol*. 2019;73(11):1336–1349. https://doi.org/10.1016/j.jacc.2019.01.017

8. Pouliot F, Shuch B, Larochelle JC, Pantuck A, Belldegrun AS. Contemporary management of renal tumors with venous tumor thrombus. *J Urol*. 2010;184(3):833–841. https://doi.org/10.1016/j.juro.2010.04.071

9. Gil-Bernabé AM, Lucotti S, Muschel RJ. Coagulation and metastasis: what does the experimental literature tell us? *Br J Haematol*. 2013;162(4):433–441. https://doi.org/10.1111/bjh.12381

10. Nierodzik ML, Karpatkin S. Thrombin induces tumor growth, metastasis, and angiogenesis: Evidence for a thrombin-regulated dormant tumor phenotype. *Cancer Cell*. 2006;10(5):355–362. https://doi.org/10.1016/j.ccr.2006.10.002

11. Fagarasanu A, Alotaibi GS, Hrimiuc R, Lee AY, Wu C. Role of extended thromboprophylaxis after abdominal and pelvic surgery in cancer patients: a systematic review and meta-analysis. *Ann Surg Oncol*. 2016;23(5):1422–1430. https://doi.org/10.1245/s10434-016-5127-1

12. 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. https://doi.org/10.1177/1076029618823288

13. Ihaddadene R, Yokom DW, Le Gal G, et al. The risk of venous thromboembolism in renal cell carcinoma patients with residual tumor thrombus. *J Thromb Haemost*. 2014;12(6):855–859. https://doi.org/10.1111/jth.12580

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