Bladder neoplasms are associated with a high frequency of painless hematuria; however, when compared with the bleeding tendencies of other solid tumors, it is arguable that this comparatively high bleeding frequency is in part the result of an ascertainment bias, given that bladder neoplasms occupy the interior of a contractile organ that is bathed with urine and whose voided contents are amenable to daily inspection and microscopic examination. The pathophysiology of hematuria in this setting likely includes organ- and tumor-specific factors, ranging from the more prosaic (eg, the vulnerability of exophytic and invasive tumors with delicate associated neoplastic vasculature to repetitive trauma from physiologic detrusor contraction during bladder emptying), to localized impairment of hemostasis, such as that caused by tumor-related fibrinolytic activity. The risk of perioperative thromboembolism associated with urothelial cancer is also probably multifactorial, with causative factors including older age, extended surgical times, venous microtrauma, and cancer-related hypercoagulability; however, the perioperative thromboembolism seen in patients with bladder cancer is not readily distinguishable from that associated with other abdominopelvic and gynecologic surgeries, including those performed for nonmalignant indications.

The clinical aspects of bleeding and thrombosis that are relevant to the management of urothelial cancer are ably addressed in the sweeping review by Fantony and Inman on page 847 of this issue of ONCOLOGY and by the associated commentaries. Intriguingly, the authors note the possibility that components of the hemostatic system warrant investigation as targets in urothelial cancer—eg, tissue factor (TF), which is expressed in nearly 80% of muscle-invasive disease and associated with a three-fold risk of death.[1]

This is an exciting time in bladder cancer research, with the recent description of the genetic signatures of a large set of muscle-invasive tumors from the Cancer Genome Atlas Network (CGAN) offering new insights into the biology of the disease.[2] And on the therapeutic front, evidence that therapeutic blockade of the programmed death (PD)-1 ligand (PD-L1) results in high-quality responses in cisplatin-refractory metastatic disease[3] suggests that a new frontier in the therapy of urothelial cancer has opened up. Epithelial-stromal interactions that predict for disease progression and resist cisplatin-based interventions—and now immunotherapeutic interventions—have not been well defined; this is a gap in our knowledge that needs to be filled. Nevertheless, TF and other components of the hemostatic system may be activated downstream of the diverse signaling pathways implicated (in the CGAN study) as potential drivers of muscle-invasive tumors—eg, genetic alterations of the EGFR family and the PI3K/Akt pathway, and chromatin-related epigenetic changes. Tumor-specific oncogenic upregulation of TF can be complemented by hypoxia-dependent upregulation of TF in tumor cells, as well as by contributions from elements of the stromal compartment, including vascular and inflammatory cells. Protease-activated receptors (PARs), including TF-VIIa-PAR2, induce immune-modulating and angiogenic cytokines, chemokines, and growth factors—resulting in a range of nonhemostatic behaviors.[4] Activation of the coagulation cascade by TF generates thrombin, and fibrin recruits platelets; together these phenomena amplify angiogenic signaling. Synergy between the coagulation system and alternative protease signaling pathways can further drive tumor growth, invasion and motility, angiogenesis, and metastases; it can also contribute to stem-like behaviors and immune escape. Therapeutic targeting of PARs is feasible, and experimental models have demonstrated proof-of-principle that targeting TF signaling attenuates tumor progression and angiogenesis.[4]

Urothelial carcinogenesis is thought to follow a two-pathway model of progression from superficial non-muscle invasive disease: a more common papillary Ta group of tumors with a low risk of
progression to muscle-invasive disease [10%] is contrasted with high-risk superficial carcinoma in situ and T1 invasive tumors with a high rate of progression to muscle invasion [50%]. While bleeding is seen in both risk groups, there is evidence to suggest that the vascular biology of the tumors in each group is distinctive.[5] It will be of translational interest to see whether differential engagement of the hemostatic system—as, for example, in the effect of TF on oncogenic drivers of low-risk and high-risk noninvasive disease—is critical to their respective angiogenic phenotypes and the risk of invasive progression.

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**References:**


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