Editorial

Improving the prognostic accuracy in renal cell carcinoma with venous thrombus with novel predictive nomograms

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Renal cell carcinoma (RCC) with venous tumor thrombus poses a therapeutic challenge in both locoregional and metastatic settings. Having in mind that the common approach in the non-metastatic setting is focused on a sophisticated invasive approach combing removal of the kidney with additional cavotomy and thrombectomy, short-term complications appear in over a half of the operated cases (1), while careful patients' selection with validated models is crucial to reach therapeutic success. Providing prognostic variables for survival in this cohort is difficult due to complexity of the matter, and well-established factors like clinical staging and pathological assessment seem to be insufficient, though. It results in possibly misleading and truly heterogeneous findings on 5-year overall survival (OS) of patients with RCC and coexisting tumor thrombus that is reported to be from 34% to 71% (2-5). Recently, some novel promising factors have emerged besides classic clinicopathological features, but also blood count-derived biomarkers, and immunohistochemical and genetic signatures (6-8).

There is growing interest in the prognostic models aimed at risk stratification in RCC patients in light of evidence that adjuvant treatment post radical surgery may change the course of the disease in localized cases (9). However, Gu *et al.* reported that postoperative adjuvant sorafenib or sunitinib was not associated with superior disease-free survival (DFS) and OS compared to controls in RCC and tumor thrombus cases (10). On the contrary, in the recent study by Baboudjian *et al.* benefit of adjuvant treatment (tyrosine kinase inhibitors or mTOR inhibitors) in terms of recurrence post thrombectomy was reported (P=0.002) (11). The CARMENA study demonstrated that sunitinib alone is not inferior to nephrectomy and adjuvant sunitinib, limiting the value of cytoreductive surgery in the metastatic setting (12). Likewise, the SURTIME trial showed that neoadjuvant sunitinib followed by nephrectomy is associated with longer OS compared to immediate cytoreductive nephrectomy (13). However, it is not clear how these findings apply to a unique group of RCC with venous thrombus, for example, if it is justified to start neoadjuvant treatment before nephrectomy with thrombectomy to limit the size of venous tumor thrombus (12). It seems that targeted molecular therapies have little influence on tumor thrombus regression, though (14). The possible solution for future systemic treatment may be then novel immunotherapy administered in specific combinations rather than a single agent-based and new prognostic models or nomograms like the one proposed by Tian *et al.* (15),

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which may be implemented for a meticulous qualification with a balanced-risk strategy.

The common problem in the majority of papers making it hard to draw definite conclusions is a relatively low volume of the studied cohorts, which is rarely >200 cases. In the recent paper by Tian *et al.*, over 14,000 cases of RCCs with venous tumor thrombus were obtained from the SEER database and supplemented with the group of 84 patients from Tongji Hospital (TJH) hospitalized between 01.2004–12.2020 with complete clinical data and adequately followed-up (15). The differences in clinical characteristics (in TJH cohort: younger patients, more advanced tumors, tumor thrombi with a higher location) between the two groups were eliminated with a propensity score matching approach. Among prognostic factors applicable for RCC with tumor thrombus one included in the previous studies e.g., clinical staging of the disease, pathological grading and histological subtypes, invasion of perirenal tissues, and both nodal and other organ metastases (16), and a consensus was established that complete excision of the thrombus improved survival (17). Here, Tian *et al.* reported significant prognostic factors for both OS (age, location of thrombus, tumor size, histological classification, nuclear grade, N stage, M stage, surgery, and systemic treatments) and cancer-specific survival (CSS; location of thrombus, size, nuclear grade, N and M stage, surgery, and systemic treatments) in multivariate Cox regression analysis (15). Then, the authors used the predefined variables to construct the respective nomograms that were characterized by greater accuracy than the TNM staging system in the assessment of the 3-year OS and CSS (15).

Another issue complicating the management of RCC with venous thrombus is the fact that approximately 1/3 of patients present with metastatic disease (18). An especially interesting group in the context of suitability for the surgical treatment is low volume metastatic disease with tumor thrombus as these individuals are considered to be possible candidates for an invasive approach. Haferkamp *et al.* reported that systemic therapy may efficiently complement radical surgery leading to an increase in survival (19). In the series by Tian *et al.* (15), the portion of metastatic cases exceeded 60%, which may serve as another argument for the extension of surgical indication for RCC cases that needs to be validated in a larger prospective setting. Finally, even M0 patients at the time of initial diagnosis surgery may further progress and this phenomenon may be possible via tumor cell expansion into the circulatory system, the potential risk of presence of cancer cells within the venous wall, and, finally, the existence of undetectable metastases (20).

Lastly, one of the major controversies is the significance of the level of tumor thrombus. Tian *et al.* reported that the location of tumor thrombus indeed affected survival, but not as significantly as tumor size, N stage, and M stage did (15). Chen *et al.* revealed no differences in CSS when comparing the patients with the thrombus located only in the renal vein and the individuals with thrombus propagating into the inferior vena cava (21). Other researchers found such a correlation, though (22), and the differences in these findings may have explanations in e.g., the selection bias. An interesting analysis of the SEER database was published recently indicating poorer results in pT3c metastatic RCC patients than in their pT3a-b cohort (23). On the other hand, the authors emphasized that the expected OS of pT3c patients was still 12 months or more with cytoreductive nephrectomy when compared with virtually 24-month OS in the latter group.

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