Nuclear Grading of Tumor Thrombus: An Unheeded Prognostic Predictor in Non-metastatic Clear Cell Renal Cell Carcinoma

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Abstract

**Background:** The prognostic risk of non-metastatic clear cell renal cell carcinoma (ccRCC) with venous tumor thrombus (VTT) is variable among individual patients following radical nephrectomy and thrombectomy. However, the prognostic potential of multiple pathological features of VTT are unexploited, and risk stratification models specific for these patients are lacking.

**Patients and methods:** This retrospective, nationwide cohort comprised 1263 non-metastatic ccRCC patients with VTT from multicentre, including Training (n=664), China-validation (n=517) and Poland-Validation cohorts (n=82). In addition to the collection of traditional clinicopathologic features, the pathologic characteristics of VTT were centrally reviewed. Independent predictors from multivariable Cox regression analysis were developed into a prognostic model. Harrell's concordance index (c-index), area under the receiver operating characteristic curve (AUC) and decision curve analysis were used to evaluate the association of the variables and prognostic models with overall survival (OS) and disease-free survival (DFS).

**Results:** Using a multi-cohort of 1263 patients, we identified that VTT grading represents an unheeded and powerful independent prognostic factor of adverse outcomes across all cohorts in multivariate analysis for OS and DFS ($P < .001$; $P < .001$; $P = .014$ in Training, China-Validation, and Poland-Validation cohorts, respectively). Moreover, VTT grading showed superiority in predicting survival risk compared with the PT grading and other indicators. A risk positioning model, named the TT-GPS score, was constructed based on four independent predictors: VTT height, VTT Grading, Perinephric fat invasion, and Sarcomatoid differentiation in primary tumor. The TT-GPS score displayed better discriminatory ability than available models in risk assessment (OS, c-index: 0.736 and 0.746, AUC: 0.828 and 0.815; DFS, c-index: 0.705 and 0.710, AUC: 0.797 and 0.787 in Training and China-Validation cohorts, respectively). Poland-Validation cohort validated the superiority of the TT-GPS score (OS, c-index: 0.840, AUC: 0.874).

**Conclusions:** VTT grading displayed superior accuracy in prediction of survival risk. By incorporating VTT grading, the TT-GPS score is a powerful predictor of adverse outcomes in non-metastatic ccRCC patients with VTT.

Introduction

One biological characteristic of renal cell carcinoma (RCC) is its propensity to extend into the venous system. Venous tumor thrombus (VTT) is observed in 4–10% of newly diagnosed RCC patients [1, 2], and surgery remains the mainstay of treatment for these patients [3]. A successful radical nephrectomy and thrombectomy provides considerable palliation to a proportion of non-metastatic RCC patients with VTT and can sometimes lead to a higher long-term survival rate [4]. However, the reported post-surgical survival varies significantly with the 5-year overall survival (OS) rate ranging from 37.0–71.0% [2, 5]. Hence, accurate risk positioning models are critically needed for these patients.

At present, most prognostic models are developed from a general population of RCC patients [4, 6–9], and not specific for non-metastatic RCC patients with VTT. Recently, E. Jason Abel developed two models with higher predictive accuracy than UISS model and SSIGN score for these patients [10, 11]. However, the reported models only analyzed one feature specific for VTT, the thrombus height.

Thrombus has long been considered as the simple extension of the primary tumor (PT) to the vessel, and thus has been assumed to have the same histopathological characteristics as the PT [1]. It has been reported recently that the grading of the clone seeding the VTT is a more important determinant of progressive competency than PT grading [12]. We wonder whether the pathological characteristics of VTT might hold largely untapped potential for risk assessment. Our analysis only focused on clear cell RCC (ccRCC) histological subtype based on the vast majority proportion of this subtype [13]. Therefore, the objective of this study is to thoroughly evaluate the risk predictive potential of multiple characteristics of VTT, especially the pathological nuclear grading of VTT (VTT grading), and to develop and validate a predictive model for the risk stratification of non-metastatic ccRCC patients with VTT following surgery.

Patients And Methods

**Patient Cohorts**

The study was approved by the institutional review board of each participating centre (ID Number: 2021NZKY-004-01), where the enrollment of patients was carried out consecutively. Following the European Association of Urology Guidelines [3], decisions about the surgical approach were made by the primary surgeon based on individual patient/tumor characteristics. Patients with previous anti-cancer therapy, history of other malignancies, lack of follow-up data, lack of pathologic specimens, and perioperative mortality (first month after surgery) were excluded from analysis. Thus, the final evaluable dataset enrolled 1263 non-metastatic ccRCC patients who underwent radical nephrectomy and thrombectomy, 664 in the Training cohort from the Eastern China Renal Cancer Collaborative Group, 517 in the China-Validation cohort and 82 in the Poland-Validation cohort (Figure 1).

Follow-up was performed according to institutional protocols, which was executed postoperatively at least every 3-6 months for the first 5 years and annually thereafter. The primary outcome was OS, defined as the interval from the date of radical surgery to the date of death from any cause, or the last follow-up period. The secondary outcome was disease-free survival (DFS), defined as the interval from the date of radical surgery to the date of radiological evidence of tumor progression, or death from any cause, or the last follow-up. All follow-ups were concluded in February 2022. All studies were conducted according to guidelines (Declaration of Helsinki) for biomedical research. This study adhered to guidelines for the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) [14] (Supplementary Table 1).
Clinical Variables

Standard preoperative assessments were similar among each institution and included laboratory and radiographic evaluation (computed tomography (CT) or magnetic resonance imaging (MRI) scans of chest, abdomen, and pelvis). Positron emission tomography/CT was utilized for suspected metastasis. Clinical variables were evaluated for each patient including age at surgery, gender, body mass index (BMI), presence of pain or hematuria, paraneoplastic syndrome (PNS) [15], hypertension, diabetes, tumor laterality, and thrombus height. The thrombus height was defined according to Mayo Clinic Classification [1]. Preoperative laboratory variables included serum creatinine, albumin, hemoglobin, and neutrophil to lymphocyte ratio (NLR). The surgical approach was tailored according to the individual patient and the thrombus height. Operative risk factors included surgical approach (open or laparoscopic), surgical time, and blood transfusion.

Pathological Variables

Pathological variables included tumor size, pathological T stage, perinephric fat invasion, presence of tumor necrosis, presence of sarcomatoid differentiation, presence of rhabdoid differentiation, and the World Health Organization/International Society of Urological Pathology (WHO/ISUP) grading [16] in PT specimens. The thrombus consistency [17], vascular wall invasion [18], presence of tumor necrosis, presence of sarcomatoid differentiation, presence of rhabdoid differentiation, and WHO/ISUP grading were evaluated in VTT specimens. VTT grading was based on the highest grading present on any slide, even if focal, as the same as PT grading. The TNM stage was determined according to the 8th edition American Joint Committee on Cancer (AJCC) classification [19]. All pathological specimens were centrally reviewed by two genitourinary pathologists (Hui Chen and Qiu Rao, with 12 years and 22 years of experience in uropathology, respectively) blinded to clinical information. When there was a different opinion, a third pathologist (Xiaojun Zhou with 43 years of experience in uropathology) re-evaluated the slice and finally reached a consensus.

Statistical Analysis

Categorical variables, normally distributed continuous variables and non-normally distributed continuous variables were reported as number and percentage, means and standard deviations, medians and interquartile ranges (IQR) respectively. The ANOVA tests were utilized to test differences between multiple groups for continuous variables assuming normal distribution and homogeneity of variance. If not, Kruskal-Wallis tests would be applied. Chi-square test and Cochran-Mantel-Haenszel (CMH) Chi-square test were used to test differences for categorical variables and ordinal variables. The Kaplan-Meier method with log-rank test was used for survival analysis and comparisons. Univariable and multivariable Cox regression analyses were performed to identify independent predictors associated with survival outcome. Factors significant on univariable cox regression were evaluated by stepwise cox regression with 0.05 for entry and 0.1 for staying. Pathological stage was excluded in the multivariable analysis because of collinearity with Mayo Clinic classification, and Spearman correlation coefficients were 0.95, 0.93 and 0.99 in three cohorts. We evaluated the discrimination or prognostic accuracy of prognostic indicators or models using Harrell’s concordance index (c-index), which is appropriate for censored data [20]. We also used time-dependent receiver operating characteristic (ROC) analysis [21] and area under the curve (AUC) to measure prognostic accuracy. The discrimination of models was compared by c-index [22] and AUC [23]. Calibration plots were generated to assess how closely the predicted outcomes approximated the actual outcomes [24]. Clinical usefulness of the prediction model was assessed by decision curve analysis (DCA) by quantifying the net benefits at different threshold probabilities [25]. All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA), except c-index, ROC, calibration plots and DCA using R 4.0.4. (R Project for Statistical Computing, Vienna, Austria).

Additional methodology is provided as Supplemental data.

Results

Clinicopathologic Characteristics of Patients

A total of 1501 non-metastatic ccRCC patients with VTT were pre-enrolled from multicentre. Based on the predefined exclusion criteria, the final evaluable dataset contained 1263 patients (Figure 1). Overall, 834 (66.03%) patients were men, and the median age was 62 years (IQR, 54-68). Following surgery, 349 (27.63%) patients were treated with cytokine therapy or targeted therapy. The median follow-up time was 54, 54, and 43 months for Training, China-Validation, and Poland-Validation cohorts, respectively. During the follow-up period, the median OS time was 70.0, 68, and 68 months for Training, China-Validation, and Poland-Validation cohorts, the median disease-free survival (DFS) time was 51 months for both Training and China-Validation cohorts. The clinicopathologic characteristics of the patients were largely balanced among three cohorts (Supplementary Table 2), except for the overwhelming proportion of patients with Mayo 0 in Poland-Validation cohort.

VTT Pathological Grading Signifies Distinct Prognosis

VTT grading was based on the highest grading present, as the same as PT grading. Comparative analysis between PT and VTT specimens across all cohorts revealed discrepancies in pathological grading (Supplementary Figure 1), although they were positively associated with each other in all three cohorts (all \( P < 0.001 \)). The VTT grading was also positively associated with tumor size, sarcomatoid/rhabdoid features in PT, PNS, perirenal fat invasion, Mayo Clinic Classification, and thrombus consistency (all \( P < 0.05 \), Supplementary Table 3), revealing that patients with higher VTT grading may represent a subgroup with an aggressive phenotype.
As expected, a higher pathological grading, for both PT and VTT, was significantly correlated with dismal prognosis in all three cohorts by Kaplan-Meier curves (all \( P < 0.001 \), Supplementary Figures 2 and 3, Supplementary Tables 4 and 5). After multivariable Cox regression analysis, PT grading failed to retain consistent significance (all \( P > 0.05 \)), however, VTT grading remained an independent predictive factor for OS (\( P < 0.001; P < 0.001; P = 0.014 \) in Training, China-Validation, and Poland-Validation cohorts, respectively Supplementary Tables 4) and DFS (all \( P < 0.001 \), Supplementary Tables 5).

Furthermore, the VTT grading showed superiority in assessing risk of outcomes compared with the PT grading and other indicators by the c-index analysis (OS: 0.671 versus 0.528-0.615, 0.678 versus 0.551-0.646, and 0.719 versus 0.511-0.700 for Training, China-Validation, and Poland-Validation cohorts, respectively; DFS: 0.663 versus 0.512-0.607, and 0.664 versus 0.531-0.630 for Training, and China-Validation cohorts, respectively; Table 1), which was confirmed by the ROC analysis (OS: AUC 0.749 versus 0.637-0.675, 0.715 versus 0.658-0.692, and 0.814 versus 0.641-0.711 for Training, China-Validation, and Poland-Validation cohorts, respectively; DFS: AUC 0.745 versus 0.593-0.674, and 0.716 versus 0.612-0.692 for Training, and China-Validation cohorts, respectively; Supplementary Figure 4). In addition, VTT grading has a higher but non–statistically significant predictive accuracy than the highest grading observed among PT and VTT by the c-index analysis (VTT grading versus the highest grading, OS: 0.674 versus 0.673 for China cohort, 0.719 versus 0.705 for Poland-Validation cohort; DFS: 0.663 versus 0.657 for China cohort). Overall, VTT grading displayed superior accuracy and discriminatory ability in predicting survival risk for non-metastatic ccRCC patients with VTT.

**Subgroup Analysis**

When analysis was restricted to patients with tumor extending to the renal vein (Mayo 0) or inferior vena cava (IVC) (Mayo I-IV), VTT grading remained an independent prognostic factor (Supplementary Figure 5-8). Additionally, the VTT grading held significance for OS and DFS within the subgroups of patients stratified by primary clinical and pathological features such as age, adjuvant therapy, tumor size, PT grading, vascular well invasion and thrombus consistency (Supplementary Figure 5-8).

**Prognostic Model TT-GPS**

Considering the underestimated and predictive role of VTT grading in risk stratification, a prognostic model incorporating VTT grading may provide a more accurate risk assessment following radical nephrectomy and thrombectomy. Hence, a simple scoring algorithm was developed using the regression coefficients from multivariable Cox analysis in Training cohort. The coefficient for each independent variables was divided by the coefficient for VTT grading, multiplied by 3 and rounded to the nearest integer. This algorithm was summarized in Table 2. We called it the TT-GPS score, indicating its four independent predictors: VTT height (Mayo Clinic classification), VTT Grading, Perinephric fat invasion, and Sarcomatoid differentiation in PT. The average TT-GPS score in this study was 2.609 (median 3, range 0 to 7). In addition, only 25 (3.8%) patients had score of 6 and 7, thus patients with score of 5 or higher were combined. Estimated OS and DFS for total patients by the TT-GPS score were shown in Supplementary Tables 6 and 7. Significant differences in OS and DFS among different scores were illustrated by Kaplan-Meier curves in independent cohorts (all \( P < 0.001 \), Figure 2).

We next compared the TT-GPS score with previously reported prognostic models, including SSIGN score [6], 2003 Leibovich score [7], UISS model [8], Karakiewicz Nomogram [4] and GRANT score [9] for the general population of RCC patients; Abel model [10] and Abel nomogram [11] specific for non-metastatic RCC patients with VTT. The C-indices of the TT-GPS score for OS were 0.736 (95% CI, 0.703-0.768), and 0.746 (95% CI, 0.711-0.780) for Training and China-Validation cohorts, respectively, which were higher than other prognostic models (Table 3). In Poland-Validation cohort, the TT-GPS score also outperformed those prognostic models in predicting OS (0.840, 95% CI, 0.791-0.889; Table 3). The superiority of the prognostic accuracy of TT-GPS score to other prognostic models was confirmed by ROC analysis (Supplementary Figure 9). Although the predicted probability of the TT-GPS score for 5-year OS and DFS had concordance comparable to that of the observed probability in all three cohorts, poor calibration of other prognostic models was observed in Poland-Validation cohort by the calibration plot (Supplementary Figure 10). Moreover, the TT-GPS score provided consistent positive and larger net benefit across abroad range of risk thresholds compared with other prognostic models by decision curve analysis (Supplementary Figure 11).

For clinical application, three-tiered risk groups were defined as low (score 0-2), intermediate (score 3,4), and high (score \( \geq 5 \)) based on the TT-GPS score by using X-tile plots [26]. Clinical survival rates were well stratified based on this simple classification (Supplementary Figure 12). Estimated OS and DFS for total patients by the TT-GPS risk classification were shown in Supplementary Tables 8 and 9. The patients in the low-risk group did not reach a median OS and DFS during follow-up. The median survival of patients in the intermediate-risk and high-risk groups was 48 and 27 months for OS, 36 and 20 months for DFS, respectively. Moreover, the TT-GPS risk classification successfully screened out low- and high-risk patients from those defined as intermediate-risk group by previously reported models (Supplementary Tables 10-13).

**Discussion**

Despite gross invasion into the venous system, not all VTT led to metastasis [12]. Hence, there is significant variability with respect to the individual progression and survival risk of non-metastatic ccRCC patients with VTT. In this regard, risk stratification for these patients is warranted for guiding postoperative surveillance and selecting patients for adjuvant therapy. However, there is no consensus on risk factors predicting the prognosis [27]. In this study, we identified that VTT grading had superior accuracy in predicting survival risk for non-metastatic ccRCC patients with VTT. Moreover, we developed and validated a novel prognostic model, the TT-GPS score, based on the VTT grading and other three routinely available clinicopathologic...
features, to improve the precision of risk positioning for these patients. To the best of our knowledge, this study analyses the largest non-metastatic ccRCC patients with VTT to date.

RCCs are notoriously heterogeneous [12], whose pathological grading varies from area to area. In routine clinical practice, tumor grading is based on the highest-grade area observed in PT. Almost all pathologic reports only describe whether there are tumor cells within VTT in common practice, and no previous reports have assessed the prognostic significance of the pathological characteristics of VTT. Our data showed for the first time that VTT grading represents an unheeded prognostic predictor and outperforms the conventional indicators, including PT grading, VTT height, and so on, in non-metastatic ccRCC with VTT. These results are consistent with the notion that the grading of the clone seeding the VTT is a more important determinant of progressive competency than PT grading [12]. However, there was no significant difference of tumor cell percentages in VTT specimens among four-tiered grading, no significant difference of Ki67 proliferative index between PT and VTT specimens, indicating that the predictive value of VTT grading is independent of tumor proliferation activity, which requires further investigation. According to our results, we suggest that VTT grading should be introduced into routine pathologic reports to provide further information about risk stratification. Inspired by the above-mentioned results, the pathological features of vein tumor thrombus might be worth exploring for prognosis prediction in other cancer types as well.

Non-metastatic ccRCC patients with VTT, belonging to locally advanced RCC, are ideal candidates for adjuvant clinical trials. Although there existed some heterogeneity in treatment after surgery which might result in different outcomes, accepting adjuvant therapy had no significance in improving the survival of patients in our study ($P > 0.05$). One persistent criticism of trial design is that there is significant heterogeneity of progression and survival risk among patients enrolled [28]. Decreasing heterogeneity within the trial population while targeting the highest risk patients may allow for easier identification of potential benefits using fewer patients. Although adjuvant clinical trials primarily seek to enroll high-risk patients, they have used risk stratification tools such as UISS model that was developed largely (86%) from low and intermediate risk patients [8, 29], whose predictive accuracy was relatively low as shown in our study. Intriguingly, TT-GPS score held the ability to further stratify patients who were already identified as intermediate-risk by conventional models, which could lead to more personalized treatment. The high-risk subgroup identified with TT-GPS score might be candidates for more aggressive strategies, possibly the adjuvant immunotherapy combined with tyrosine kinase inhibitor therapy. In addition, the TT-GPS score is simple to calculate. All score components are routinely available clinical and pathologic features, negating the need for additional expertise or training, demonstrated by the external validation in Poland-Validation cohort.

Our study is not devoid of limitations. The retrospective nature introduces the risk of measurement and ascertainment biases due to non-standard follow-up. Nonetheless, this more closely reflects real-world practice, making the conclusions of the study more generalizable. Following prospective validation, the VTT grading and TT-GPS score has the potential to be indispensable in risk stratification and clinical trial enrollment for non-metastatic ccRCC patients with VTT in the future. Since the TT-GPS score is developed and validated only for clear cell histology, further work is needed to expand the score on papillary histology and compare it with the VENUSS score [30] for risk stratification.

**Conclusions**

In conclusion, non-metastatic RCC patients with VTT have high but variable risk of progression and may possess improved prognosis from accurate risk assessment. Using multicentre contemporary data, we show that VTT grading represents an unheeded prognostic predictor. Moreover, the TT-GPS score we developed and validated allows for accurate risk positioning, outperforms previously reported models. Further validation of the TT-GPS score is currently underway in different ethnic populations to confirm its value and suggest its introduction into routine pathologic reports.

**Abbreviations**

ccRCC: clear cell renal cell carcinoma; VTT: venous tumor thrombus; c-index: Harrell’s concordance index, AUC: area under the receiver operating characteristic curve; OS: overall survival; DFS: disease-free survival; PT: primary tumor; TRIPOD: the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis; CT: computed tomography; MRI: magnetic resonance imaging; BMI: body mass index; PNS: paraneoplastic syndrome; NLR: neutrophil to lymphocyte ratio; WHO/ISUP: the World Health Organization/International Society of Urological Pathology; AJCC: American Joint Committee on Cancer; IQR: interquartile ranges; DAC: decision curve analysis; IVC: inferior vena cava;

**Declarations**

**Acknowledgments**

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**Authors’ contributions**

Le Qu, Wenquan Zhou, Jingping Ge, and Linhui Wang contributed to the conception and/or design of the study. All authors participated in the acquisition, analysis, and interpretation of data. All authors were involved in the drafting and revision of the manuscript, and all authors approved the
final version of the manuscript for publication. Wenquan Zhou, Jingping Ge, Linhui Wang, Xiang Feng, Benkang Shi, Shaogang Wang, Junhua Zheng, Wei Xue, Ming Chen, Hongqian Guo, Xiongbing Zu, Weijin Qin, Jun Jiang, Haifeng Wang, Dan Xia, Ning Xu, Chaozhao Liang, Gongxian Wang, Yixun Liu, Hongwei Zhao, Jianning Wang, Jiwen Cheng, Zhiyu Liu, Lukasz Zapałł, Zhe Wang, Xiaojun Zhou contributed to the administrative, technical, or material support.

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**Ethical Approval and Consent to participate**

The present study was approved by the Medical Ethics Committee of Jinling Hospital of Medical School of Nanjing University and other participating centres (ID Number: 2021NZKY-004-01). Written informed consent was obtained from all subjects.

**Consent for publication**

Written informed consent for publication was obtained from all participants.

**Competing interests**

The authors declare that they have no competing interests.

**References**


Tables

Table 1. Concordance index analysis of the prognostic accuracy of potential variables in indicated cohorts.
<table>
<thead>
<tr>
<th>Variables</th>
<th>OS</th>
<th>DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Training cohort</td>
<td>China-Validation cohort</td>
</tr>
<tr>
<td></td>
<td>(n = 664)</td>
<td>(n = 517)</td>
</tr>
<tr>
<td>C-index (95% CI)</td>
<td>P</td>
<td>C-index (95% CI)</td>
</tr>
<tr>
<td>VTT grading</td>
<td>0.671 (0.638-0.704)</td>
<td>0.678 (0.642-0.715)</td>
</tr>
<tr>
<td>PT grading</td>
<td>0.615 (0.580,0.649)</td>
<td>0.006</td>
</tr>
<tr>
<td>Sarcomatoid features in PT</td>
<td>0.603 (0.576-0.631)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sarcomatoid features in VTT</td>
<td>0.552 (0.529-0.574)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vascular wall invasion</td>
<td>0.528 (0.494-0.561)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thrombus consistency</td>
<td>0.545 (0.512-0.579)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Perirenal fat invasion</td>
<td>0.578 (0.547-0.609)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PNS</td>
<td>0.561 (0.528-0.594)</td>
<td>&lt;0.001</td>
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<tr>
<td>Tumor size</td>
<td>0.548 (0.509-0.587)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pathological T stage</td>
<td>0.609 (0.574-0.643)</td>
<td>0.012</td>
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<tr>
<td>Thrombus levela</td>
<td>0.612 (0.576,0.647)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

aAccording to the Mayo Clinic Classification [1]

Abbreviations: PT, primary tumor; VTT, venous tumor thrombus; PNS, Paraneoplastic Syndrome; CI, confidential interval; NA, not available; OS, overall survival; DFS, disease-free survival.

Table 2. TT-GPS score algorithm.
<table>
<thead>
<tr>
<th>Variables</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>VTT height&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>I</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>2</td>
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<tr>
<td>IV</td>
<td>2</td>
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<tr>
<td>Pathological grading in VTT&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>I</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>0</td>
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<tr>
<td>III</td>
<td>2</td>
</tr>
<tr>
<td>IV</td>
<td>3</td>
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<tr>
<td>Perinephric fat invasion</td>
<td></td>
</tr>
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<td>No</td>
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<td>Yes</td>
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<tr>
<td>Sarcomatoid differentiation in PT</td>
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<tr>
<td>No</td>
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<tr>
<td>Yes</td>
<td>1</td>
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</table>

Abbreviations: PT, primary tumor; VTT, venous tumor thrombus.

<sup>a</sup>According to the Mayo Clinic Classification [1]

<sup>b</sup>According to the World Health Organization/International Society of Urological Pathology (WHO/ISUP) grading criterion [16]

**Table 3.** Concordance index analysis of the prognostic accuracy of the TT-GPS score and previously reported prognostic models in indicated cohorts.
<table>
<thead>
<tr>
<th>Prognostic model</th>
<th>OS Training cohort (n = 664)</th>
<th>China-Validation cohort (n = 517)</th>
<th>Poland-Validation cohort (n = 82)</th>
<th>DFS Training cohort (n = 664)</th>
<th>China-Validation cohort (n = 517)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C-index (95% CI)</td>
<td>C-index (95% CI)</td>
<td>C-index (95% CI)</td>
<td>C-index (95% CI)</td>
<td>C-index (95% CI)</td>
</tr>
<tr>
<td>TT-GPS score</td>
<td>0.736 (0.703-0.768)</td>
<td>0.746 (0.711-0.780)</td>
<td>0.840 (0.791-0.889)</td>
<td>0.705 (0.677-0.733)</td>
<td>0.710 (0.677-0.742)</td>
</tr>
<tr>
<td>SSIGN score</td>
<td>0.607 (0.570-0.643)</td>
<td>&lt;0.001</td>
<td>0.630 (0.589-0.670)</td>
<td>&lt;0.001</td>
<td>0.718 (0.611-0.826)</td>
</tr>
<tr>
<td>Leibovich score</td>
<td>0.648 (0.614-0.683)</td>
<td>&lt;0.001</td>
<td>0.668 (0.630-0.705)</td>
<td>&lt;0.001</td>
<td>0.704 (0.610-0.797)</td>
</tr>
<tr>
<td>UISS model</td>
<td>0.629 (0.600-0.658)</td>
<td>&lt;0.001</td>
<td>0.648 (0.615-0.680)</td>
<td>&lt;0.001</td>
<td>0.732 (0.642-0.822)</td>
</tr>
<tr>
<td>GRANT score</td>
<td>0.616 (0.580-0.651)</td>
<td>&lt;0.001</td>
<td>0.632 (0.592-0.672)</td>
<td>&lt;0.001</td>
<td>0.696 (0.613-0.780)</td>
</tr>
<tr>
<td>Karakiewicz Nomogram</td>
<td>0.665 (0.631-0.699)</td>
<td>&lt;0.001</td>
<td>0.677 (0.637-0.717)</td>
<td>&lt;0.001</td>
<td>0.672 (0.656-0.779)</td>
</tr>
<tr>
<td>Abel model</td>
<td>0.648 (0.613-0.683)</td>
<td>&lt;0.001</td>
<td>0.674 (0.637-0.712)</td>
<td>&lt;0.001</td>
<td>0.714 (0.629-0.800)</td>
</tr>
<tr>
<td>Abel nomogram</td>
<td>0.643 (0.604-0.681)</td>
<td>&lt;0.001</td>
<td>0.640 (0.595-0.684)</td>
<td>&lt;0.001</td>
<td>0.698 (0.598-0.798)</td>
</tr>
</tbody>
</table>

Abbreviations: TT-GPS, VTT height, VTT Grading, Perinephric fat invasion, Sarcomatoid differentiation in PT; SSIGN, the Mayo Clinic Stage, Size, Grade and Necrosis; UISS, the University of California Los Angeles Integrated Staging System; GRANT, the Grade, Age, Nodes and Tumor; CI, confidential interval; OS, overall survival; DFS, disease-free survival.

**Figures**
Figure 1


Figure 2

The diagrams illustrate the statistical significance levels for different cohorts, with P values less than 0.001.
Kaplan-Meier estimates of OS (upper; \( P<0.001 \)) and DFS (lower; \( P<0.001 \)) stratified by the TT-GPS score in (A) Training cohort, (B) China-Validation cohort, and (C) Poland-Validation cohort (only OS). OS, overall survival; DFS, disease-free survival; TT-GPS, VTT height, VTT Grading, Perinephric fat invasion, Sarcomatoid differentiation in PT.

**Supplementary Files**

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- 02Supplementarymaterials.docx