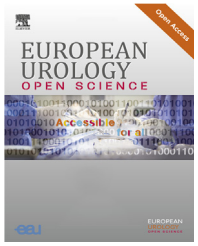
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Kidney Cancer

Assessment of the VENUSS and GRANT Models for Individual Prediction of Cancer-specific Survival in Surgically Treated Nonmetastatic Papillary Renal Cell Carcinoma

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Abstract

Background: Guidelines recommend VENUSS and GRANT models for the prediction of cancer control outcomes after nephrectomy for nonmetastatic papillary renal cell carcinoma (pRCC).
Objective: To test the ability of VENUSS and GRANT models to predict 5-yr cancer-specific survival in a North American population.
Design, setting, and participants: For this retrospective study, we identified 4184 patients with unilateral surgically treated nonmetastatic pRCC in the Surveillance, Epidemiology, and End Results database (2004–2019).
Outcome measurements and statistical analysis: The original VENUSS and GRANT risk categories were applied to predict 5-yr cancer-specific survival. A cross-validation method was used to test the accuracy and calibration of the models and to conduct decision curve analyses for the study cohort.
Results and limitations: The VENUSS and GRANT categories represented independent predictors of cancer-specific mortality. On cross-validation, the accuracy of the VENUSS and GRANT risk categories was 0.73 and 0.65, respectively. Both models

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showed good calibration and performed better than random predictions in decision curve analysis. Limitations include the retrospective nature of the study and the absence of a central pathological review.

Conclusion: VENUSS risk categories fulfilled prognostic model criteria for predicting cancer-specific survival 5 yr after surgery in North American patients with non-metastatic pRCC as recommended by guidelines. Conversely, GRANT risk categories did not. Thus, VENUSS risk categories represent an important tool for counseling, follow-up planning, and patient selection for appropriate adjuvant trials in pRCC.

Patient summary: We tested the ability of two validated methods (VENUSS and GRANT) to predict death due to papillary kidney cancer in a North American population. The VENUSS risk categories showed good performance in predicting 5-year cancer-specific survival.

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1. Introduction

Among surgically treated kidney cancer cases, 25% are non–clear-cell renal cell carcinoma (nccRCC). Papillary RCC (pRCC) is the commonest nccRCC subtype [1]. Most pRCC cases harbor nonmetastatic disease and are treated with radical nephrectomy (RN) or partial nephrectomy (PN) [2–4]. Several prognostic models comprising clinical and pathological RCC variables are recommended by international guidelines for prediction of disease recurrence and mortality after nephrectomy [5–8]. Of these, two European models were developed and validated to predict cancer control outcomes after RN or PN in nonmetastatic pRCC [9]: VENUSS [10–12] and GRANT [12–14]. However, their ability to predict cancer-specific survival (CSS) has not been validated in a North American population. We addressed this knowledge gap using the 2004–2019 Surveillance, Epidemiology, and End Results (SEER) database [15]. Data on cancer recurrence, which represented the original endpoint for both the VENUSS and GRANT models, are not available in this database. Thus, we tested the magnitude of the association between the risk categories in the models (VENUSS: low, intermediate, and high risk; GRANT: favorable and unfavorable risk) and 5-yr CSS. Using the correlation coefficients obtained, we tested the ability of the models to predict 5-yr CSS on cross-validation. We hypothesized that both models would demonstrate a high degree of accuracy and correlation between predicted and observed 5-yr CSS rates, and that both would outperform random predictions in decision curve analysis (DCA) [16].

Table 1 – Summary of VENUSS and GRANT prognostic models for unilateral surgically treated non-metastatic papillary renal cell carcinoma tested in the present study.

Prognostic model	Prognostic factors	Scoring	Classes
VENUSS	**Size**		
	≤4 cm	0	
	>4 cm	2	
	T stage		
	T1	0	
	T2	1	**Low risk:** 0–2 points
	T3–4	2	**Intermediate risk:** 3–5 points
	N stage		**High risk:** ≥6 points
	N0/X	0	
	N1	3	
	Grade		
	G1–2	0	
	G3–4	2	
	Venous tumor thrombus		
	Absent	0	
	Present	2	
	Age at diagnosis		
	>60 yr	1	
	≤60 yr	0	
GRANT	**T stage**		
	T1–3a	0	**Favorable risk:** 0-1 points
	T3b,c–T4	1	**Unfavorable risk:** ≥2 points
	N stage		
	N0/X	0	
	N1	1	
	Grade		
	G1–2	0	
	G3–4	1	

2. Patients and methods

2.1. Patient selection

We used the SEER database (2004–2019) to identify patients with unilateral nonmetastatic pRCC (International Classification of Disease for Oncology site code C64.9 and histology code 8260/3 [17]) aged ≥18 yr who were treated with either RN or PN. We only included patients fulfilling criteria that were subsequently used to generate the VENUSS and GRANT risk categories (Table 1, Supplementary Fig. 1). VENUSS risk categories were defined according to the following criteria: tumor size (≤4 cm vs >4 cm), T stage (T1 vs T2 vs T3–4), N stage (N0/X vs N1), grade (G1–2 vs G3–4), and the presence of venous tumor thrombus (absent vs present). GRANT risk categories were defined according to age at diagnosis (>60 yr vs ≤60 yr), T stage (T1–3a vs T3b,c–T4), N stage (N0/X vs N1), and grade (G1–2 vs G3–4). The endpoint of interest was 5-yr CSS (death from RCC).

2.2. Statistical analyses

Twentyfold cross-validation was performed. Specifically, the overall population was randomly divided into 20 cohorts. Among these cohorts, one was selected as the validation cohort. We applied VENUSS risk categories to the remaining patients and quantified the regression coefficients for intermediate and high risk relative to low risk for prediction of cancer-specific mortality (CSM). We then applied these coefficients

to the validation cohort to quantify their accuracy in predicting CSS at 5 yr after nephrectomy. We repeated these steps 20 times, selecting all the cohorts as the validation cohort one at a time. Accuracy was generated for the cross-validation model-derived probability for every subject and was quantified using Heagerty's concordance index [18]. The individual 5-yr CSS predictions were then plotted against the actual 5-yr CSS observed and calibration plots were generated. Finally, DCAs were conducted to quantify the performance of the VENUSS model relative to random predictions of CSS. The same development and validation steps (accuracy, calibration and DCA) were used for 5-yr CSS prediction according to the GRANT risk categories. All statistical tests were two-sided, with the level of significance set at $p < 0.05$. Tests were performed using R v4.1.3 (R Foundation for Statistical Computing, Vienna Austria) [19].

3. Results

3.1. Descriptive characteristics

We identified 4184 patients with unilateral surgically treated nonmetastatic pRCC who fulfilled the criteria for the VENUSS and GRANT prognostic models (Table 2). Overall, 69%, 24%, and 7.1% of the patients were classified as having VENUSS low, intermediate, and high risk, while 75% and 25% were classified as having GRANT favorable and unfavorable risk, respectively.

According to the VENUSS risk categories, 5-yr CSS rates were 97% for the low-risk, 92% for the intermediate-risk, and 63% for the high-risk group ($p < 0.001$; Fig. 1B). According to the GRANT risk categories, 5-yr CSS rates were 96% for the favorable-risk and 85% for the unfavorable-risk group ($p < 0.001$; Fig. 1C).

Table 2 – Descriptive characteristics of 4184 patients diagnosed with nonmetastatic papillary renal carcinoma between 2004 and 2019 in the Surveillance, Epidemiology, and End Results database

Parameter	Result
Median age at surgery, yr (IQR)	62 (55–69)
Male, *n*(%)	3163 (76)
Year of diagnosis, *n*(%)	
2004–2011	1681 (40)
2012–2019	2503 (60)
Partial nephrectomy, *n*(%)	2142 (51)
Disease grade, *n*(%)	
G1	472 (11)
G2	2209 (53)
G3	1406 (34)
G4	97 (2.3)
T stage, *n*(%)	
T1	3263 (78)
T2	504 (12)
T3	384 (9.2)
T4	33 (0.8)
Median tumor size, mm (IQR)	36 (25–55)
Perinephric or renal sinus fat invasion, *n*(%)	277 (6.7)
Presence of thrombus, *n*(%)	103 (2.5)
N1 disease, *n*(%)	238 (5.7)
VENUSS risk category, *n*(%)	
Low risk	2882 (69)
Intermediate risk	1004 (24)
High risk	298 (7.1)
GRANT risk category, *n*(%)	
Favorable risk	3144 (75)
Unfavorable risk	1040 (25)
Median follow-up, yr (IQR)	4.9 (2.1–8.8)

IQR = interquartile range.

3.2. Application of VENUSS and GRANT risk categories to predict 5-yr CSS

Regarding VENUSS, regression models predicting CSM revealed hazard ratios of 2.7 for the intermediate-risk group and 13.1 for the high-risk group with the low-risk group as the reference (Table 3). Both variables achieved independent predictor status. VENUSS-predicted 5-yr CSS rates derived from regression model were 97%, 91%, and 64% for the low-, intermediate-, and high-risk groups, respectively. Regarding GRANT, regression models predicting CSM revealed a hazard ratio of 3.6 for the unfavorable-risk group with the favorable-risk group as the reference and achieved independent predictor status. GRANT-predicted 5-yr CSS rates derived from regression model were 96% and 85% for the favorable-risk and unfavorable-risk groups, respectively.

3.3. Accuracy, calibration, and DCA

After twentyfold cross-validation, application of the VENUSS coefficients for prediction of 5-yr CSS resulted in accuracy of 0.73 (Table 3). A calibration plot showed virtually perfect agreement between individual predicted and observed 5-yr CSS in the low-risk (predicted CSS 97%, observed CSS 96%; difference of 1%) and intermediate-risk (predicted CSS 91%, observed CSS 88%; difference of 3%) groups. Conversely, overestimation in the high-risk group (predicted CSS 64%, observed CSS 50%; difference of 14%) was observed (Table 3, Supplementary Fig. 2A). VENUSS-derived predictions exhibited a net benefit on DCA (Fig. 2).

After twentyfold cross-validation, application of the GRANT coefficients for prediction of 5-yr CSS resulted in accuracy of 0.65 (Table 3). A calibration plot showed virtually perfect agreement between individual predicted and observed 5-yr CSS in both the favorable-risk (predicted CSS 96%, observed CSS 94%; difference of 2%) and unfavorable-risk (predicted CSS 85%, observed CSS 84%; difference of 1%) groups (Table 3, Supplementary Fig. 2B). GRANT-derived predictions exhibited a net benefit on DCA.

4. Discussion

Accurate prediction of cancer control outcomes in patients with RCC is important for counseling, follow-up planning, and patient selection for appropriate adjuvant trials. Despite the high prevalence of nccRCC, it is still unclear which prognostic model better predicts oncological outcomes after surgery according to histological subtype. Specifically, VENUSS and GRANT prognostic models are guideline-recommended for prediction of cancer control outcomes after surgical treatment for nonmetastatic pRCC [9]. The VENUSS prognostic model was specifically developed for prediction of pRCC recurrence at 5 yr after surgery. Conversely, the GRANT prognostic model was developed for prediction of recurrence and overall survival rates at 5 yr after surgery in a cohort that included different histological subtypes. To date, the ability of these models to predict CSS at 5 yr after surgery in pRCC has never been tested and compared in a contemporary population-based North American cohort. We addressed this knowledge gap and hypothesized

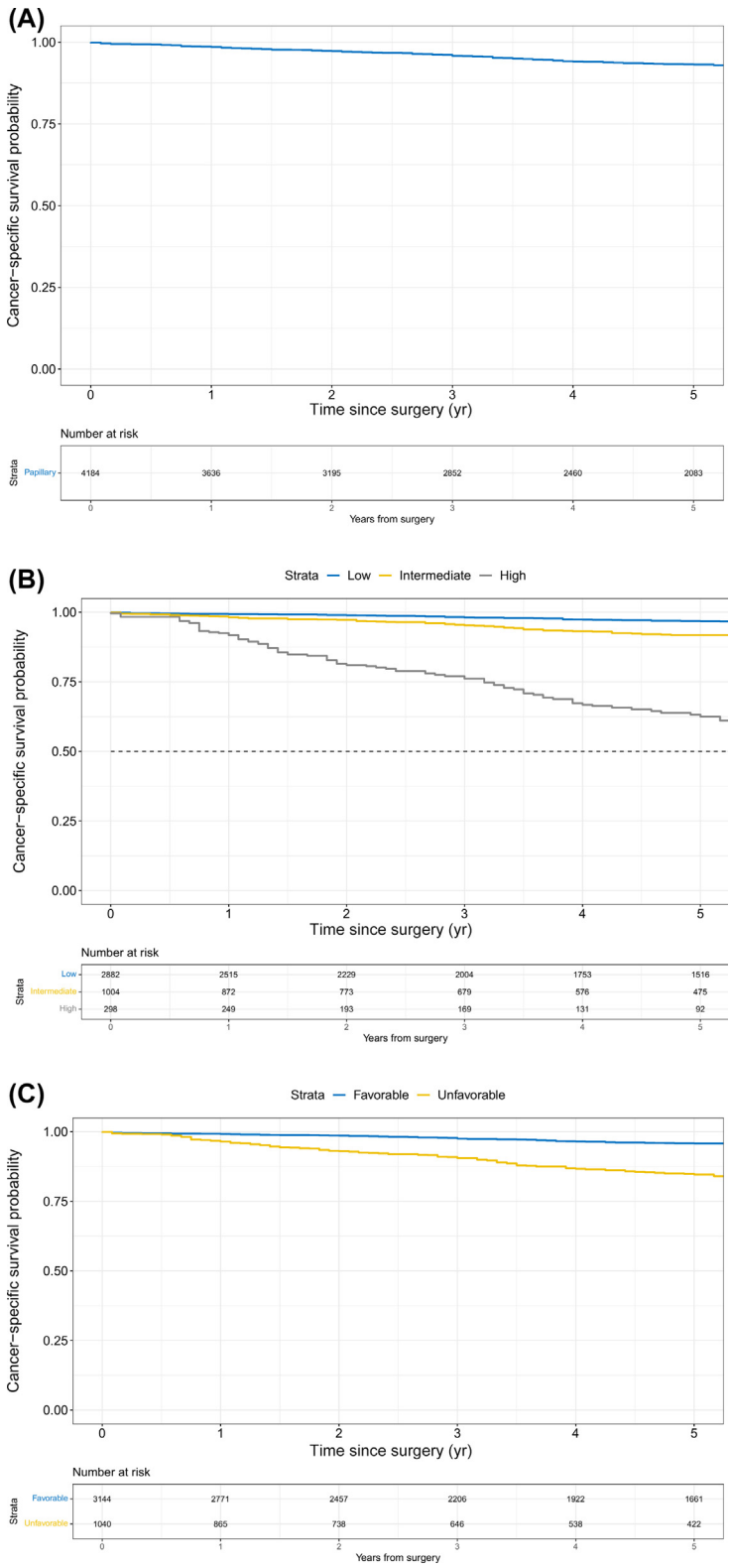


Fig. 1 – Kaplan–Meier plots with log-rank test comparing cancer-specific survival over 5 yr among patients with unilateral surgically treated nonmetastatic papillary renal carcinoma diagnosed in 2004–2019 as reported in the Surveillance, Epidemiology, and End Results database (A) overall and by (B) VENUSS and (C) GRANT risk categories.

that both models would demonstrate an equally high degree of accuracy in predicting 5-yr CSS for North American patients relative to the original results. Our study revealed several important findings.

First, to the best of our knowledge, this is the first population-based North American analysis addressing 5-yr CSS predictions using VENUSS or GRANT risk categories. Moreover, the present study is based on the largest sample

Table 3 – Univariable Cox regression models predicting 5-yr CSS according to VENUSS and GRANT risk categories for patients with surgically treated nonmetastatic papillary renal cell carcinoma diagnosed between 2004 and 2019 as recorded in the Surveillance, Epidemiology, and End Results database

	Univariable Cox regression		5-yr CSS (%)			Patients,
	HR (95% CI)	*p* value	Predicted	Observed	c index[a]	*n* (%)
VENUSS risk category					0.73	
Low risk	Reference		97	96		2882 (69)
Intermediate risk	2.7 (2.0–3.6)	**<0.001**	91	88		1004 (24)
High risk	13.1 (9.9–17.3)	**<0.001**	64	50		298 (7.1)
GRANT risk category					0.65	
Favorable risk	Reference		96	94		3144 (75)
Unfavorable risk	3.6 (2.9–4.5)	**<0.001**	85	84		1040 (25)

CI = confidence interval; CSS = cancer-specific survival; HR = hazard ratio.
[a] After cross-validation.

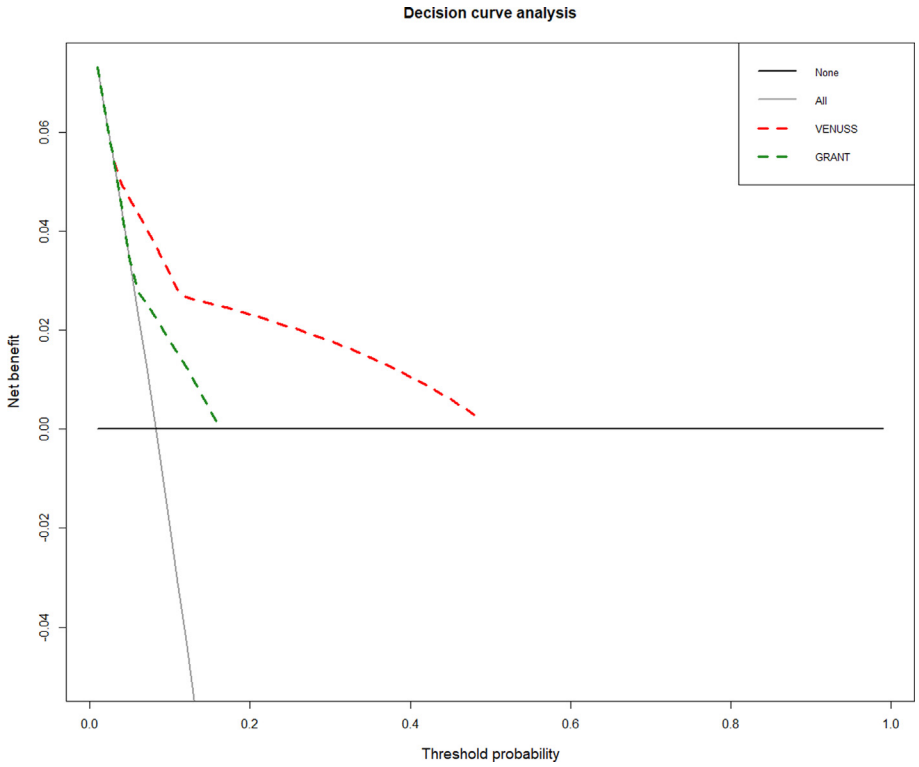


Fig. 2 – Decision curve analyses for the VENUSS and GRANT prognostic models. Assuming that patients with papillary renal cell carcinoma would be treated differently (eg, would be included in adjuvant systemic therapy trials), the net benefit of VENUSS and GRANT are plotted against threshold probabilities. Strategies putting all or none into an adjuvant systemic therapy trial are denoted. VENUSS showed a better net benefit for threshold probabilities between 10% and 50% and proved to be more useful than simple observational data on cancer-specific survival in papillary renal cell carcinoma. Conversely, the GRANT prognostic model showed a much more limited net benefit.

size on which these analyses have been performed to date. Sample size is particularly relevant when less frequent histological subtypes such as pRCC are examined. Moreover, a large sample size is also important when CSS is high, since mortality events may be too infrequent in smaller populations. Finally, the current sample represents the most contemporary population with nonmetastatic surgically treated pRCC. It is of note that the original development cohorts used to define the VENUSS and GRANT prognostic models were both smaller and more historical than the current study population. Specifically, the VENUSS prognostic model was developed by Klatte et al. [10] using a multi-institutional European pRCC cohort (n = 556; year of diagnosis 2000–2016). The GRANT prognostic model was developed by Passalacqua et al. [13] using a multi-institutional European cohort of patients with all RCC subtypes in an adjuvant systemic therapy trial (n = 303; year of diagnosis 1994–2006). As a result, there are remarkable differences in the distribution of demographic, clinical, and pathological characteristics between the present cohort and the validation cohorts. Specifically, our cohort had more favorable pathological features versus the VENUSS validation cohort in terms of T stage (T1: 78% vs 66%; T3: 9.2% vs 22%), median tumor size (36 vs 40 mm), and perinephric or renal sinus fat invasion (6.7% vs 17%). These differences are reflected in the distribution of patients across VENUSS risk categories (low risk: 69% vs 64%; intermediate risk: 24% vs 24%; high risk: 7.1% vs 12% in our cohort vs the orig-

inal VENUSS cohort). A similar phenomenon can be observed in the study by Erdem et al. [11] validating the disease recurrence prediction ability of the VENUSS model in a different European cohort of 980 patients with pRCC. These differences corroborate the need for testing and comparing the ability to predict CSS with VENUSS or GRANT risk categories in a large contemporary population-based North American pRCC cohort. This step is crucial before clinical implementation of these models for North American patients with surgically treated nonmetastatic pRCC.

Second, the VENUSS risk categories predicted 5-yr CSS with accuracy of 0.73 after cross-validation. This accuracy exceeds the minimum threshold of 0.70 [20]. Moreover, calibration plots for the VENUSS risk categories demonstrated virtually perfect agreement between predicted and observed 5-yr CSS in the low- and intermediate-risk groups. Conversely, there was overestimation in comparison to ideal prediction in the high-risk group. The VENUSS risk categories also demonstrated a clear net benefit on DCA. Specifically, assuming that patients with pRCC would be treated differently (eg, they would be included in adjuvant systemic therapy trials), the net benefit of VENUSS was plotted against threshold probabilities and strategies assigning all patients or none to an adjuvant systemic therapy trial. VENUSS showed better net benefit between threshold probabilities of 10% and 50% was more useful than simple observational data on CSS in pRCC. When the same endpoints were applied to GRANT, substantially lower accuracy was observed (0.65). Thus, the calibration properties and DCA of the GRANT model are irrelevant since its use for prediction of 5-yr CSS in the North American population cannot be recommended on the basis of the current results. However, it should be noted that both models were initially devised to predict cancer recurrence. Therefore, it is possible that in a North American database reporting recurrence data, they could yield better accuracy and equally good calibration for recurrence-free survival as an outcome. This represents the main limitation of the current study. The National Cancer Data Base (NCDB) cannot be used to assess the model accuracy in predicting cancer-specific outcomes since no data on CSS or cancer recurrence are available. Overall mortality does not represent an adequate endpoint in surgically treated nonmetastatic pRCC, as an important proportion of such patients would succumb to other-cause mortality. Finally, it is unlikely that institutional databases would provide sufficiently large sample sizes for analyses of recurrence and CSS in a contemporary cohort.

Taken together, our observations indicate that the VENUSS risk categories are sufficiently accurate, are well calibrated, and provide a net benefit on DCA. Conversely, the GRANT risk categories did not meet these criteria. Therefore, VENUSS can be recommended for use in North American clinical practice, while GRANT cannot.

To the best of our knowledge, our findings cannot be compared with other studies as we are the first to test the ability of VENUSS and GRANT risk categories to predict 5-yr CSS for North American patients. However, Rosiello et al. [12] tested the accuracy of VENUSS and GRANT in predicting 5-yr CSS in pRCC using a European pRCC cohort from a single institution (n = 312, diagnosed during 1987–2019). Interestingly, 5-yr CSS rates for the VENUSS high-risk category were 43% in their cohort and 63% in our study. It is likely that this non-negligible difference is driven by the higher proportion of patients with N1 disease (10% in the Rosiello cohort vs 5.7% in our study). Lymph node invasion is strongly associated with CSM in pRCC [21]. The authors reported accuracy values for both the VENUSS and GRANT models (VENUSS: 0.85; GRANT: 0.84) [12]. However, their findings are based on a substantially smaller sample size and more historical observations, in addition to a selective focus on European patients. Similarly, in the VENUSS model validation performed by Erdem et al [11], the 5-yr CSS rate for the high-risk group differed remarkably from the rate observed in our cohort (44% vs 63%). It is likely that this non-negligible difference was driven by the higher proportion of patients with T3–4 disease (20% in the Erdem cohort vs 10% in our study) and incidence of tumor thrombus (4% in the Erdem cohort vs 2.5% in our study). The VENUSS model achieved a c index of 0.79 for prediction of disease recurrence in the study by Erdem et al [11]. As previously discussed, the cohort had more frequent unfavorable pathological features and thus higher variability in patient distribution. As a result, pronounced differences between study cohorts could have led to substantial differences in discrimination ability [22]. Moreover, lower accuracy in the present study versus the validation be Erdem et al. (0.73 vs 0.79) is highly probable when predictions of a relatively infrequent event such as CSM in pRCC and of an invariably more frequent event such as disease recurrence are compared.

Despite its novelty, our study is not devoid of limitations. First, SEER is a retrospective database with the potential for selection biases. However, observational databases such as SEER and NCDB represent the only opportunity to study less frequent primary tumors, especially in advanced stages. Second, no central review of pathological stage and histological subtype was applied in the SEER database. Third, as previously discussed, the lack of information on time to recurrence prevented us from evaluating recurrence-free survival outcomes in addition to 5-yr CSS. Fourth, the SEER database lacks information on the hereditary origin of pRCC or the binephric status of patients. However, multiple factors render the number of hereditary conditions marginal at best, and a relevant impact on analyses is highly unlikely. The absence of bilateral disease reduces the probability of hereditary conditions in our cohort. In addition, hereditary RCC accounts for 1–4% of RCC cases [22]. Therefore, the impact of these aggressive primary tumors in our unilateral pRCC cohort should be marginal, if present. Finally, the SEER database does not provide information on the frequency of follow-up or adherence to follow-up schedules.

5. Conclusions

VENUSS risk categories fulfilled prognostic model criteria for predicting cancer-specific survival 5 yr after surgery in North American patients with nonmetastatic papillary renal cell carcinoma as recommended by guidelines. Conversely, GRANT risk categories did not. Thus, VENUSS risk categories represent an important tool for counseling, follow-up plan-

ning, and patient selection for appropriate adjuvant trials in pRCC.

Author contributions: Mattia L. Piccinelli had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Piccinelli, Karakiewicz.
Acquisition of data: Piccinelli, Tian.
Analysis and interpretation of data: Piccinelli, Tian, Karakiewicz.
Drafting of the manuscript: Piccinelli, Tappero, Cano Garcia, Barletta, Incesu, Morra, Scheipner, Karakiewicz.
Critical revision of the manuscript for important intellectual content: Luzzago, Mistretta, Ferro, Saad, Shariat, Ahyai, Longo, Tilki, Briganti, Chun, Terrone, de Cobelli, Musi, Karakiewicz.
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Appendix A. Supplementary data

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