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ORIGINAL ARTICLE

Nephrometry scores to predict oncological outcomes following partial nephrectomy (UroCCR Study 70)

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Abstract

Purpose Partial nephrectomy (PN) for large or complex renal tumors can be difficult and associated with a higher risk of recurrence than radical nephrectomy. We aim to evaluate the clinical useful of nephrometry scores for predicting oncological outcomes in a large cohort of patients who underwent PN for renal cell carcinomas.

Methods Our analysis included patients who underwent PN for renal cell carcinoma in 21 French academic centers (2010–2020). RENAL, PADUA, and SPARE scores were calculated based on preoperative imaging. Uni- and multivariate cox models were performed to identify predictors of recurrence-free survival and overall survival. The area under the curve (AUC) was used to identify models with the highest discrimination. Decision curve analyses (DCAs) determined the net benefit associated with their use.

Results A total of 1927 patients were analyzed with a median follow-up of 32 months (14–45). RENAL score ($p = 0.01$), age ($p = 0.002$), histological type ($p = 0.001$), high nuclear grade ($p = 0.001$), necrotic component ($p < 0.001$), and positive margins ($p = 0.005$) were significantly related to recurrence in multivariate analyses. The discriminative performance of the 3 radiological scores was modest (65, 63, and 63%, respectively). All 3 scores showed good calibration, which, however, deteriorated with time. Decision curve analysis of the three models for the prediction of overall and recurrence-free survival was similar for all three scores and of limited clinical relevance.

Conclusion The association between nephrometry scores and oncological outcomes after NP is very weak. The use of these scores for predicting oncological outcomes in routine practice is therefore of limited clinical value.

Keywords Partial nephrectomy · Nephrometry score · Predicting · Recurrence

Introduction

Partial nephrectomy (PN) is the standard of care for treating localized renal cell carcinoma (RCC) [1]. It provides equivalent oncological control and better preserves renal function than radical nephrectomy [2, 3].

Over time, this procedure has been extended to larger renal masses, thus constantly pushing back the limits of nephron sparing surgery. However, PN for large or complex renal tumors can be difficult and associated with a higher risk of recurrence than RN [4–6]. Therefore, determining the risk of recurrence in this scenario to choose the best surgical approach and to inform the patient preoperatively is necessary.

To standardize the description of renal tumor's complexity, objective anatomical classification systems, such as PADUA [7], RENAL [8], and, most recently, Simplified Padua Renal (SPARE) nephrometry scores [9], have been described. These systems can assist the surgeon in the decision-making process and in planning the most appropriate surgical approach. However, the data remain conflicting

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regarding the prediction of oncological outcomes, with some studies suggesting that scores were associated with worse oncological outcomes [10–12], while others failed to confirm these findings.

The aim of this study was to evaluate the clinical useful of nephrometry scores for predicting oncological outcomes in a large cohort of contemporary patients who underwent PN for renal cell carcinomas.

Methods

Data source and study population

All patients in this study were prospectively enrolled in the UroCCR multicentric database (UroCCR project (NCT03293563), which is IRB approved and obtained the CNIL authorization number DR-2013-206). We conducted a retrospective analysis of all patients who underwent PN for a localized kidney cancer at 21 departments of urology between 2010 and 2020. Patients whose follow-up was less than 6 months were excluded of the analysis, as well as patients presenting multifocal tumors, benign tumors, secondary tumors of the kidney, those whom radiological data were unavailable, and those who presented an N + or M + status at staging or on final histological analysis.

Nephrometry scores

Nephrometry scores were calculated from preoperative computed tomography (CT) scan or magnetic resonance imaging (MRI) performed up to 90 days before surgery. The scores were calculated based on the criteria published by the team that initially reported them.

Covariates

Patients and tumor characteristics were collected in an electronic database. Demographics included age, gender, ECOG performance status, American Society of Anesthesiologists (ASA) score, and body mass index (BMI). Tumor characteristics included tumor size, tumor side, histological subtype, ISUP grade, margin status, tumor necrosis, and sarcomatoid component.

Follow-up protocol and outcome

Follow-up schedules were specific to each institution, but most patients had a physical examination, abdominal imaging with CT scan imaging, and chest imaging every 6 months. The primary end point of model prediction was disease-free survival (DFS), defined as the time from surgery to disease recurrence (including local and distant recurrences) or death from any cause. Local recurrence (defined as recurrence in the bed resection or recurrence in the renal fossa) or metastatic recurrence and death (related to cancer or not) were specified after analysis of medical records.

Statistical analysis

Statistical analyses as well as reporting and interpretation of the results were conducted according to established guidelines and consisted of three steps. First, cox models were used to perform both univariate and multivariable analyses to identify predictors of DFS and OS. For each outcome, we generated three different models, including RENAL, PADUA, and SPARE scores. Multivariable models included only covariates meeting a $p < 0.2$ level of significance at univariate analysis. Second, performance of nephrometry scores was evaluated in terms of discrimination and calibration. Discrimination (the ability to discern patients who will experience an event from those who will not) was quantified using the concordance index (c-index) as described by Uno et al. for specific time points and by Harrell et al. for global time assessment. Calibration (the ability to make predictions as close as possible from the occurrence of real events) was assessed by the Brier score. The Brier score is the mean of the square of the difference between predicted and observed probabilities: a score of 0 indicates perfect calibration and 1 is the worst possible calibration. Finally, Decision curve analysis (DCA) was used to determine whether the clinical value of the scores increased the net benefit over a realistic range of threshold probabilities. A two-sided p value of < 0.05 defined statistical significance. All statistical analyses were performed with STATA 15.1 (StataCorp, College Station, TX, USA).

Results

Patients' characteristics

Clinical, radiographic, and pathological characteristics of patients are summarized in Table 1. A total of 1927 patients were analyzed. Median age was 59 years (IQR: 51–68) and BMI was 27 (23.9–30.1). 432 (22%) patients underwent open surgery, 1491 (78%) laparoscopic surgery among whom 1280 (86%) was robot assisted. Median RENAL, PADUA, and SPARE scores were 7 (IQR: 6–9), 9 (IQR: 7–10), and 2 (IQR: 1–5), respectively. Median tumor size was 4 cm (2.5–5). 1285 (71%) tumors were clear cell carcinoma, 279 (15%) were papillary carcinoma, and 128 (7%) were chromophobe carcinoma. Regarding grading, 1052 (63%) tumors were low Fuhrman grade, 1493 (84%) tumors were pT1 stage, 69 (4%) were pT2 stage, and 217 (12%)

Table 1 Patient, operative, and tumor characteristics of 1927 patients included in this analysis

Variable	*n*	
Gender *n* (%)		
Male	1927	1322 (68.6)
Female		605 (31.4)
Median age (y) (IQR)	1891	59 (51–68)
Median BMI (kg/m^2) (IQR)	1927	27.4 (23.9–30.1)
ECOG score *n* (%)		
0	1782	1434 (80.47)
1		282 (15.82)
2		58 (3.25)
3		8 (0.45)
ASA score *n* (%)		
1	1810	513 (28.34)
2		994 (54.92)
3		294 (16.24)
4		9 (0.5)
Surgical approach *n* (%)		
Open	1923	432 (22.46)
Coelioscopic		211 (10.97)
Robot assisted		1280 (66.56)
Prior abdominal surgery *n* (%)		
Yes	1927	640 (33.21)
No		1287 (66.79)
Tumor size (cm) median (IQR)	1927	4 (2.50–5.0)
NSS indication *n* (%)		
Elective	1927	1672 (86.77)
Imperative		255 (13.23)
Side *n* (%)		
Left	1927	920 (47.74)
Right		1007 (52.26)
Tumor histology *n* (%)		
Clear cell	1822	1285 (70.53)
Papillary type 1		210 (11.53)
Papillary type 2		69 (3.79)
Chromophobe		128 (7.03)
Other		130 (7.14)
pT *n* (%)		
pT1	1779	1493 (83.92)
pT2		69 (3.88)
pT3		217 (12.2)
Fuhrman grade *n* (%)		
Low (1–2)	1668	1052 (63.07)
High (3–4)		616 (36.93)
Fat invasion *n* (%)		
Yes	1651	165 (9.99)
No		1486 (90.01)
Lymphovascular invasion *n* (%)		
Yes	1645	99 (6.02)
No		1546 (93.98)
Tumor necrosis *n* (%)		
Yes	1804	363 (20.12)
No		1441 (79.88)
Surgical margins *n* (%)		
Negative	1714	1590 (92.77)
Positive		124 (7.23)
Sarcomatoid component n (%)		
Yes	1797	66 (3.67)
No		1731 (96.33)
Median RENAL score (IQR)	1927	7 (6–9)
Median PADUA score (IQR)	1927	9 (7–10)
Median SPARE score (IQR)	1927	2 (1–5)

tumors were pT3 stage. Surgical margins were positive for 124 (7.2%) tumors. Median follow-up was 32 months (14–45). Recurrence occurred for 151 patients. Local recurrence occurred for 66 patients: 45 in the bed resection, 19 in the renal fossa, and 2 in both sites. Metastatic recurrence occurred for 103 patients. The recurrence sites were lung (51 patients), retroperitoneal lymph nodes (16 patients) mediastinal lymph nodes (16 patients), liver (14 patients), bones (14 patients), adrenal glands (13 patients), pancreas (5 patients), brain (3 patients), skin (2 patients), and pleura (2 patients). Thirty-one patients died from recurrence or treatment. Median time to recurrence was 20 months (12–31). The recurrence sites in relation to early and late recurrences and RENAL score are shown in Table 2.

Predictors of DFS

On univariate analysis age, ECOG performance status (PS), clear cell RCC histology, nuclear grade, sarcomatoid features, tumor necrosis, perinephric or sinus fat invasion, positive surgical margins, tumor size, RENAL score, PADUA score, and SPARE score were all associated with an increased risk for recurrence (all $p < 0.05$) (Table 3).

After adjusting for age, ECOG PS, clear cell RCC histology, nuclear grade, sarcomatoid features, tumor necrosis, perinephric or sinus fat invasion, positive surgical margins, and tumor size, only RENAL score (HR = 1.12, [CI 95% 1.04–1.20]; $p = 0.002$) was found to be associated with the occurrence of recurrences.

The discriminative performance of each of the three models is shown in Fig. 1a. The RENAL, PADUA, and SPARE models achieved a c-index of 65% (95% CI [61–72]), 63% (95% CI [60–69]), and 63% (95% CI [60–69]), respectively, which is quite modest (Fig. 1a). Next, we used the integrated Brier score to assess calibration of radiological models over a time interval of 60 months. All models showed good calibration with low integrated Brier scores (all integrated brier

Table 2 Recurrence sites in relation to early and late recurrences and Renal score (all $p > 0.05$)

	Early recurrence (≤ 12 months)			Late recurrence (> 12 months)		
	Renal score			Renal score		
	Low	Intermediate	High	Low	Intermediate	High
Local[a]	7	17	8	7	17	10
Metastatic[a]						
Lung	5	11	8	4	10	13
Retroperitoneal lymph nodes	1	4	0	1	6	4
Mediastinal lymph nodes	0	4	2	1	4	5
Liver	3	5	1	0	4	1
Bones	2	3	4	2	0	3
Adrenal glands	0	3	2	2	3	3
Pancreas	0	0	0	1	2	2
Brain	0	0	0	0	2	1
Skin	0	1	0	0	1	0
Pleura	1	0	0	0	1	0

[a]Some patients had both local and metastatic recurrence, and some metastatic recurrences were in several sites

Table 3 Univariate and multivariable regression analyses predicting disease-free survival in patients treated with partial nephrectomy

	Univariable analysis		Multivariable analysis: model RENAL		Multivariable analysis: model PADUA		Multivariable analysis: model SPARE	
	Haz. ratio (95% CI)	*p*	Haz. ratio (95% CI)	*p*	Haz. ratio (95% CI)	*p*	Haz. ratio (95% CI)	*p*
Age	1.02 (1.01–1.04)	< 0.001	1.02 (1.01–1.03)	0.002	1.02 (1.01–1.03)	0.002	1.02 (1.01–1.03)	0.001
ECOG PS (0 vs > 1)	1.49 (1.08–2.06)	0.01	1.18 (0.82–1.69)	0.3	1.19 (0.83–1.71)	0.3	1.14 (0.81–1.62)	0.4
Robotic approach	1.07 (0.66–1.72)	0.8						
Clear cell RCC histology	1.79 (1.27–2.51)	0.001	1.91 (1.28–2.85)	0.001	1.92 (1.27–2.91)	0.002	1.98 (1.32–2.95)	0.001
Nuclear grade (1–2 vs 3–4)	2.63 (1.98–3.49)	< 0.001	1.74 (1.24–2.43)	0.001	1.73 (1.24–2.45)	0.001	1.74 (1.25–2.43)	0.001
Sarcomatoid features	4.86 (3.11–7.62)	< 0.001	2.02 (1.21–3.41)	0.008	1.99 (1.17–3.41)	0.01	2.11 (1.26–3.55)	0.004
Tumor necrosis	3.01 (2.25–4.01)	< 0.001	2.43 (1.72–3.43)	< 0.001	2.39 (1.69–3.38)	< 0.001	2.44 (1.74–3.44)	< 0.001
Perinephric or sinus fat invasion	1.26 (1.02–1.54)	0.02	1.21 (0.95–1.52)	0.11	1.21 (0.95–1.53)	0.11	1.21 (0.95–1.52)	0.12
Microvascular invasion	1.01 (0.81–1.27)	> 0.9						
Positive Surgical margins	1.95 (1.25–3.05)	0.003	1.91 (1.21–3.01)	0.005	1.81 (1.12–2.91)	0.01	1.93 (1.23–3.04)	0.004
Tumor size	1.04 (1.02–1.07)	< 0.001	0.97 (0.89–1.06)	0.7	1.01 (0.93–1.07)	0.9	0.99 (0.93–1.06)	0.9
RENAL score	1.22 (1.13–1.32)	< 0.001	1.13 (1.02–1.24)	0.01				
PADUA score	1.16 (1.07–1.25)	< 0.001			1.05 (0.96–1.16)	0.2		
SPARE score	1.09 (1.02–1.16)	0.005					1.04 (0.96–1.12)	0.3

ECOG Eastern Cooperative Oncology Group; *RCC* renal cell carcinoma; *CI* confidence interval

scores < 0.15). However, there was a deterioration of calibration over time in all models (Fig. 1c). Figure 2a represents decision curves that show the clinical usefulness of radiological scores to predict recurrences. The results are presented as a graph with the selected probability threshold. We found that the curves of the three radiological models (RENAL, PADUA, SPARE) were very close regardless of the selected threshold and the recorded net benefit was consistently low regardless of the prediction strategy.

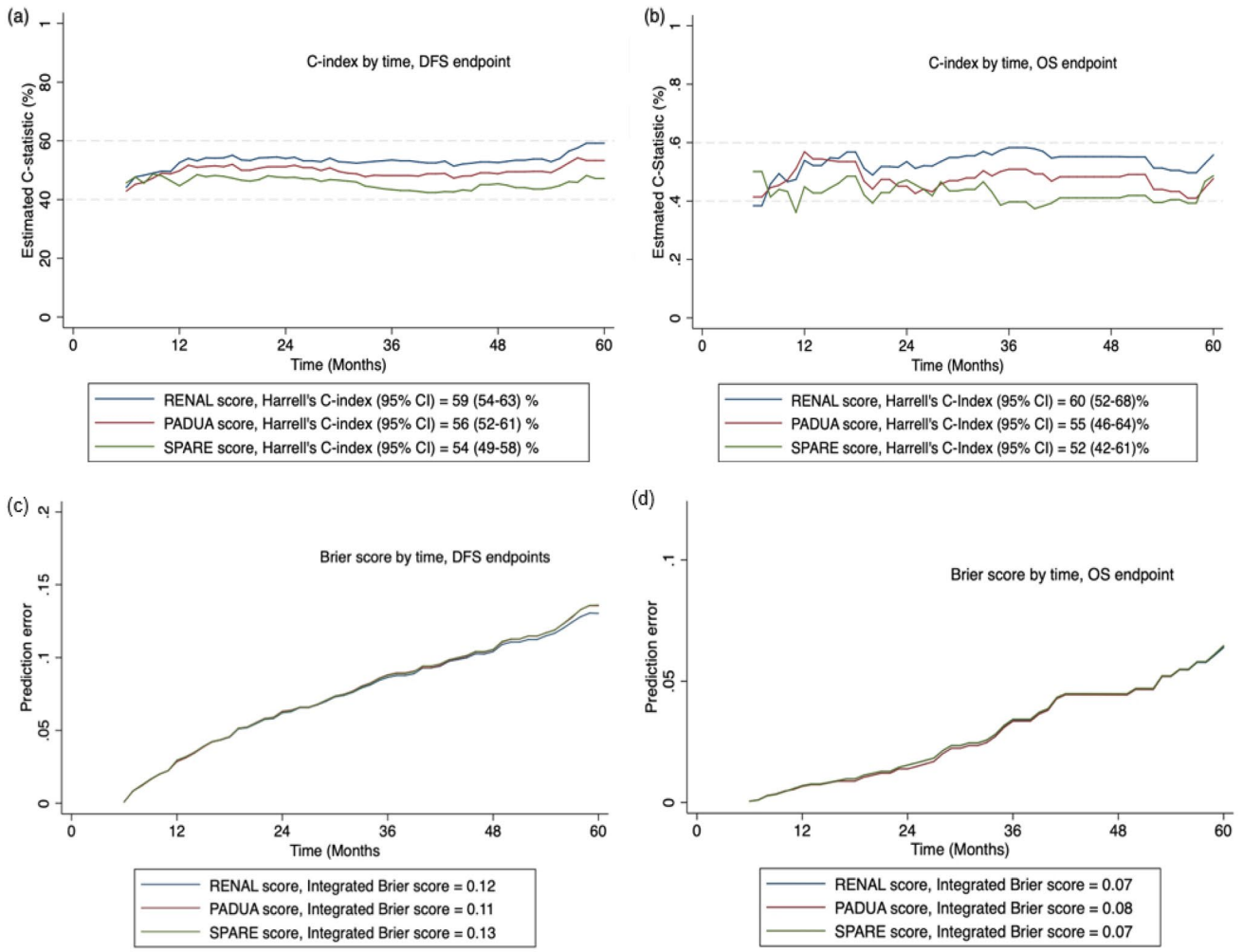

Fig. 1 Model discrimination measures for each time t: DFS (**a**) and OS (**b**) and prediction error curves show the Brier score for each time t: DFS (**c**) and OS (**d**)

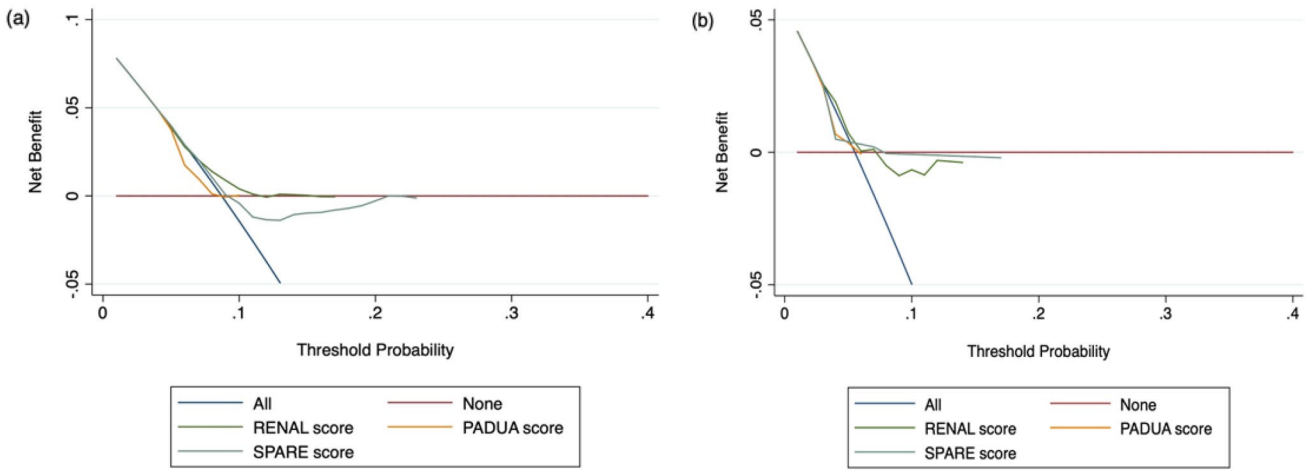

Fig. 2 Decision curve analysis demonstrating the clinical net benefit associated with the use of nephrometry scores at 36 months predicting **a** DFS and **b** OS

Predictors of OS

Univariate and multivariate cox analyses were carried out to identify independent predictors of mortality after PN. In univariate analysis age, ECOG PS, sarcomatoid features, and RENAL score were significant predictors of mortality. After adjusting for covariables, RENAL score remained associated with the risk of death contrary to PADUA and SPARE score. Regarding discrimination, the performance of all models was poor: the RENAL, PADUA, and SPARE models achieved a c-index of 65% (95% CI [61–72]), 63% (95% CI [60–69]), and 63% (95% CI [60–69]), respectively (Fig. 1b). In terms of calibration, all models showed good calibration with low integrated Brier scores (all integrated Brier scores < 0.1) (Fig. 1d). However, there was again a deterioration of calibration over time in all models. Finally, the decision curve analysis demonstrated poor net benefit of all nephrometry scores (Fig. 2b).

Discussion

In the management of localized renal cancer, preserving kidney function is paramount whenever feasible. Consequently, PN has emerged as the standard surgical approach for localized RCC. While the advent of advanced surgical tools like surgical robots enables us to undertake more intricate surgeries, the oncological safety of the procedure should never be compromised. Over the last 10 years, several scores have been reported to better describe tumor complexity and estimate perioperative outcomes [7–9]. The most popular are the RENAL (radius, exophytic/endophytic, nearness, anterior/posterior, location) and PADUA (preoperative aspects and dimensions used for an anatomical) scores, and more recently the simplified PADUA Renal (SPARE) score. These scores are derived from preoperative imaging of large historical databases. Their ability to predict oncological outcomes after PN is debated: some studies suggested they can predict worse outcomes, while others failed to confirm these findings [10, 11, 13–15].

In our study, DFS and OS were associated with RENAL nephrometry score, but were not linked with the PADUA and SPARE Models. However, the discriminative performance of the RENAL score was suboptimal, evidenced by a concordance index of approximately 63%. In addition, we made a decision curve analysis (DCA—a statistical method that addresses the question whether we have the ability to make a better decision with or without a score). As described by Vickers [16], we estimated the benefit that consists in the subtraction of the proportion of all patients who are false positive from the proportion who are true positive, weighted by the relative harm of a false-positive and false-negative result. Our analyses showed a very modest net benefit for all scores.

Many predictive factors of recurrence after surgery in patients with RCC have been reported, and of anatomical tumor characteristics, tumor size has been identified as predictive of recurrence in many studies [17, 18]. In the present study, we decided to adjust our models considering tumor size. This adjustment ensures that we account for this variable, which might otherwise overshadow the results, potentially making the overall score appear significant solely due to the tumor size.

While pathological attributes might offer more reliable prognostic indicators, they are typically accessible only post-surgery, limiting their preoperative utility. Pre-surgery tumor biopsies present their own challenges, notably their non-diagnostic rate and questionable negative predictive value [19]. However, radiomic analysis has shown potential in predicting recurrence. For instance, a multicenter study by Yang et al. highlighted that patient with lower radiomic scores faced a 4.44 times greater risk of recurrence compared to those with higher score [20].

Interestingly, while the RENAL score was significantly correlated with recurrence post-partial nephrectomy, PADUA and SPARE scores were not. This might be because the tumor's position concerning the renal poles (the 'L' component in the RENAL score) is more crucial than its lateral or medial position, as assessed by the PADUA and SPARE models. Kikushi et al. [21] found that the location relative to the polar line was associated with the Ki67 index in clear cell renal cell carcinoma, and Kutikov et al. [22] showed that location in relation to the renal poles (L; $p = 0.002$) was associated with high-grade features, supporting our findings.

The strength of our study is the large sample size of patients from several institutions, the comprehensive evaluation considering most recent scores, and a rigorous approach that included the assessment of discrimination, performance, and clinical utility. However, it is not without limitations. The multicenter, retrospective, national database design might introduce declarative biases. The lack of centralized radiological reviews and the varied expertise of performing surgeons might affect perioperative results. Additionally, the relatively short follow-up could result in missed local or metastatic recurrence detections. Nonetheless, according to some literature, the median time to recurrence after RAPN is between 13.1 and 20 months [14].

Conclusion

In this large cohort of patients with localized renal masses undergoing PN, nephrometry scores do not seem to predict oncological outcomes in daily practice. However,

these scores should continue to be used for perioperative outcomes.

Author contributions ML contributed to project development, data collection and management, and manuscript writing. J-CB was involved in data management. C-KB, PB, AV, M-LL, ND, PP, FA, F-XN, BP, TT, CC, MB, GP, J-AL, MD, MV, TW, RB, RT, and IO: collected data. JO was responsible for project development, data management, and manuscript editing. Z-EK was responsible for project development, data management, data analysis, and manuscript editing.

Data availability Data are available on specific request.

Declarations

Conflict of interest None.

Ethical standards The present study identified as the UroCCR 70 ancillary project was approved by the internal review board (CNIL DR 2013-206; NCT03293563). All patients included in this registry signed informed consent. This study also guaranteed compliance at all times with the Jardé Law on Research including Humans (November 16, 2016, French Government) and the Declaration of Helsinki.

Informed consent All patients included in this registry and the UroCCR project (CNIL DR 2013-206; NCT03293563) signed informed consent.

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