Local Recurrence After R0 Partial Nephrectomy for RCC: Insights from a Large Multicenter Cohort (PREPARE study – UroCCR 140)

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Lucas Deluegue*[1], Gaëlle Margue[2,3], Laurine Cadart[4], Jean-Christophe Bernhard[2,3], Karim Bensalah[5], Pierre Bigot[6], Nicolas Doumerc[7], Franck Bruyere[8], Morgan Roupret[9], Nicolas Branger[10], Louis Surlemont[11], Cécile Champy[12,13], Bastient Parier[14], Philippe Paparel[15], Thibaut Waeckel[16], Hervé Lang[17], Constance Michel[18], Alexis Fontenil[19], Jean-Baptiste Beauval[20], Jean-Jacques Patard[21], Maxime Vallee[22], Julien Guillotreau[23], Olivier Traxer[24], Laurent Guy[25], François Audenet[26], Benjamin Rouget[27], Jonathan Olivier[1,28], Jean-Christophe Fantoni[1].

1 : Urology Department, Hôpital Claude Huriez, CHU Lille, Lille, France
2 : Urology Department, CHU Bordeaux, Bordeaux, France
3 : I.CaRe Bordeaux - BRIC INSERM U1312, Université de Bordeaux, Bordeaux, France
4 : Department of Epidemiology and Biostatistics, CHU Lille, Lille, France
5 : Urology Department, CHU Rennes, Rennes, France
6 : Urology Department, CHU Anger, Anger, France
7 : Urology Department, CHU Toulouse, Toulouse, France
8 : Urology Department, CHU Tours, Tours, France
9 : Sorbonne University, GRC5 Predictive Onco-Uro, AP-HP, Urology, Pitie-Salpetriere Hospital, F-75013 Paris, France
10 : Urology Department, Institut Paoli Calmettes, Marseille, France
11 : Urology Department, CHU Rouen, Rouen, France
12 : Urology Department, CHU Henri Mondor, APHP, Creteil, France
13 : Inserm, Clinical Investigation Center 1430, Henri Mondor University Hospital, AP-HP, 94000 Creteil, France
14 : Urology Department, Hôpital Bicêtre, APHP, Paris, France
15 : Urology Department, CHU Lyon Sud - Hospices Civils de Lyon, Lyon, France
16 : Urology Department, CHU Caen, Caen, France
17 : Urology Department, CHU Strasbourg, Strasbourg, France
18 : Urology Department, Hôpital privé St Joseph, Paris, France
19 : Urology Department, CHU Nîmes, Nîmes, France
20 : Urology Department, Clinique la croix du sud, Toulouse, France
21 : Urology Department, CH Mont de Marsant, Mont de Marsant, France
22 : Urology Department, CHU Poitiers, Poitiers, France
23 : Urology Department, Clinique Pasteur, Toulouse, France
24 : Urology Department, Hôpital Tenon, APHP, Paris, France
25 : Urology Department, CHU Clermont-Ferrand, Clermont-Ferrand, France
26 : Urology Department, Hôpital Européen Georges Pompidou, APHP, Paris, France
27 : Urology Department, CH Libourne, Libourne, France
28 : University Lille, CNRS, INSERM, CHU Lille, Institut Pasteur de Lille, UMR9020-U1277-CANTHER-Cancer Heterogeneity Plasticity and Resistance to Therapies, F-59000, Lille, France

* corresponding author:
lucasdeluegue@outlook.fr.
0649233143.
Service d'urologie, Hôpital Claude Huriez, CHU de Lille 59037 Lille.

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Abstract

Purpose:

Local recurrence after partial nephrectomy with negative margins (R0) remains a clinical concern in the management of non-metastatic renal cell carcinoma (RCC). We aimed to quantify its incidence and to identify independent predictors of recurrence in a large, contemporary, multicenter cohort.

Methods:

We retrospectively analyzed 2,438 patients from the UroCCR database who underwent R0 nephron-sparing surgery for cT1–cT3a/N0/M0 RCC between 2007 and 2022 across 24 French centers. The primary endpoint was histologically confirmed local recurrence (tumor bed or ipsilateral renal recurrence). Fine-and-Gray competing-risk regression, with death treated as a competing event, was applied to determine independent predictors.

Results:

After a median follow-up of 66 months (IQR:26-86), local recurrence occurred in 97 patients (3.9%). Independent predictors included open surgery (sHR 2.25 [95% CI, 1.02-4.97]), intraoperative complications (sHR 4.00 [95% CI, 1.65-9.68]), longer delay between diagnosis and surgery (sHR 1.02 [95% CI, 1.003-1.04]), clear cell histology (sHR 4.12 [2.18–7.79]), higher RENAL score, vascular emboli (sHR 3.90 [95% CI, 1.67-9.08]), and tumor necrosis (sHR 2.62 [95% CI, 1.54-4.47]). Robotic assistance was associated with a reduced recurrence risk (sHR 0.50 [95% CI, 0.28-0.88]).

Conclusion:

Local recurrence after R0 partial nephrectomy, though infrequent, is associated with clinical, surgical, and pathological factors. Open surgery, intra-operative complications, treatment delay, tumor complexity, vascular emboli, necrosis and clear-cell histology were correlated with an increase risk of recurrence.

Purpose

Renal cancer remains relatively common, with 431,288 new cases and 179,368 deaths reported worldwide in 2020 [1]. For localized disease, surgical resection remains the standard of care [2]. When technically feasible, nephron-sparing surgery (NSS) offers oncologic outcomes comparable to radical nephrectomy for renal tumors regardless of the surgical approach [3,4]. In addition to equivalent cancer control, NSS confers better preservation of renal function [5].

While the benefits of NSS are well established, the risk of oncological failure after R0 resection, particularly in the form of local recurrence, continues to raise concern among clinicians. Understanding the determinants of such recurrence is essential for improving patient selection, refining surgical techniques, and guiding follow-up strategies. Studies have already been conducted on predictive factors for recurrence, but questions remain regarding factors in the subset of patients with negative margins only. Therefore, there remains a need for large-scale, robust analyses to clarify these risks.

Despite negative margins, local recurrence can impact prognosis and follow-up, underscoring the need for robust risk stratification. We analyzed its incidence and predictors after R0 partial nephrectomy in a large multicentre cohort.

Methods

Study design and population:

This retrospective cohort study used the prospectively maintained UroCCR database (NCT03293563), approved by the relevant institutional review boards (Comité de Protection des Personnes Sud-Ouest et Outre-mer III, decision DC 2012/108) and the French data-protection authority (CNIL DR-2013-206). All participants gave written informed consent. There are no funding for this project or for the collection of UroCCR data.

We included consecutive adults (≥18 years) who underwent NSS with negative margins for clinically localised RCC (cT1–cT3a/N0/M0) between April 2007 and November 2022 in 24 French centres. Exclusion criteria were: history of ipsilateral/contralateral RCC surgery, multifocal tumors, benign lesions or renal metastases of other primaries, missing key data or <6 months of follow-up.

Data collection:

Baseline variables comprised age, sex, body-mass index (BMI), smoking status, comorbidities (including chronic kidney disease define by estimated glomerular filtration less than 60 ml/min/1.73m^2), baseline estimated glomerular filtration rate, and ECOG performance status. Surgical variables included approach (open, conventional laparoscopy, robot-assisted laparoscopy), tumor size, RENAL nephrometry score, and intra-operative complications. Pathology variables covered histological subtype, Fuhrman grade, presence of necrosis, vascular or perirenal fat invasion, sarcomatoid or cystic components.

Tumors were staged using the 2017 TNM classification and typed according to the 2016 WHO system [6,7]. Post-operative imaging followed French Association of Urology guidelines and was risk-adapted using the University of California Integrated Staging System (UISS) [8,9].

Surgical approach:

Surgical procedures included open surgery, standard laparoscopic surgery, or robot-assisted laparoscopic NSS. The choice of approach was left to the discretion of the surgeon, based on tumor size, location, complexity, as well as institutional expertise.

Outcomes:

The primary outcome was histologically proven local recurrence in the tumor bed or ipsilateral kidney. The time of follow-up as measured from surgery to local recurrence, death or censoring (31 December 2023).

The secondary outcome was the identification of predictors of local recurrence.

Prognostic factors evaluated:

Based on published literature, the following potential prognostic variables were assessed in univariate analysis: age, tumor size, delay between diagnosis and surgery, estimated intraoperative blood loss, occurrence of intraoperative complication, surgical approach (open vs. laparoscopic), use of robotic assistance, tumor histology, Fuhrman grade, presence of vascular emboli, preoperative biopsy, tumor location, presence of necrosis and/or sarcomatoid component, papillary and microcystic architecture, RENAL nephrometry score, and ECOG performance status.

Statistical analysis:

Categorical variables were described using frequencies and percentages, while continuous variables were expressed as mean ± standard deviation or median with interquartile range (IQR), depending on data distribution. Normality was assessed both visually and using the Shapiro–Wilk test.

The 10-year cumulative incidence of local recurrence was estimated using the Kalbfleisch and Prentice method, accounting for death as a competing event. Prognostic factors associated with local recurrence were assessed using the Fine and Gray subdistribution hazard model for competing risks, with death treated as a competing risk.

The proportional hazards assumption for each potential predictor was evaluated Schoenfeld residuals plots. In the case of non-proportionality, the time was divided into two separated periods (0 to 5 years vs 5 to 10 years follow-up periods). Log-linearity for continuous covariates was assessed using cubic spline function; non-linear variables were categorized accordingly.

Variables with a p-value <0.05 in univariate analyses were considered for multivariable modeling using a backward stepwise selection procedure. Regarding the literature about impact of tumor size on recurrence, tumor size was forced into the multivariable model. Multicollinearity was checked using the variance inflation factor (VIF).

Missing data were handled under the ‘missing at random’ hypothesis using multiple imputation with chained equations (MICE), generating 20 imputed datasets. Rubin’s rules were applied to pool estimates across imputations [10].

To evaluate robotic assistance, we initially compared robotic assisted versus non-robotic procedures (regardless of the surgical approach). Given the potential confounding effect of the surgical approach (open vs. laparoscopic), we performed an additional univariate analysis comparing laparoscopic versus robotic-assisted laparoscopic procedures.

Statistical significance was set at a two-sided p-value <0.05. All analyses were performed using SAS software (SAS Institute, Cary, NC, version 9.4).

Results

Of 3,012 eligible patients, 574 were excluded (Figure 1), leaving 2,438 for analysis. Full demographic and tumor characteristics are presented in Table 1. The median follow-up was 66 months [IQR: 26–86]. During this period, 97 patients (3.9%) experienced a local recurrence, 59 (60.8%) at the site of the treated lesion and 38 (39.2%) are new lesion in the ipsilateral kidney. Among the recurrences, 30 (30.9%) occurred within the first five years, while 67 (69.1%) occurred after five years. Concerning recurrences after five years, 37 were in the low UISS group (55%). The mean time to recurrence was 76 months.
The study cohort included 1655 (67.9%) men and 783 women (32.1%), with a median age at diagnosis of 61 years [IQR 57;74], and a median BMI of 26.7 kg/m^2 [IQR 23.9;30.1]. The majority of patients (87.5%) underwent minimally invasive surgery (MIS), with 78.7% of procedures performed using robotic assistance. Open surgery was performed in 304 cases (12.5%). The median time from diagnosis to surgery was 2 months [IQR 1;4].

Predictive factors:

Univariate analysis (Table 2) identified several factors significantly associated with an increased risk of local recurrence. Notably, tumor necrosis (sHR 2.78 [95% CI, 1.84–4.20], $p < 0.0001$) and the presence of a sarcomatoid component (sHR 4.60 [2.18–9.68], $p < 0.0001$) were strong predictors. Vascular emboli were also highly significant within the first 5 years following diagnosis (sHR 6.28 [2.68–14.68], $p < 0.0001$), although their impact beyond 5 years was not statistically significant (sHR 1.72 [0.80–3.66], $p = 0.16$).

A longer interval between diagnosis and surgery was associated with a slight but significant increase in recurrence risk (sHR 1.02 [1.01–1.03], $p = 0.003$). Tumor size was also a key factor: tumors measuring 4–7 cm (sHR 2.41 [1.60–3.65], $p < 0.0001$) and >7 cm (sHR 2.52 [1.15–5.52], $p = 0.021$) carried a higher risk compared to tumors <4 cm.

The RENAL score, categorized as low, intermediate, or high, demonstrated a stepwise association with recurrence risk. Compared to low scores, intermediate (sHR 1.85 [1.14–

3.01], p = 0.013) and high scores (sHR 2.95 [1.65–5.28], p = 0.0003) were associated with significantly increased risk.

Intraoperative complications markedly elevated the recurrence risk within 5 years (sHR 6.58 [2.81–15.42], p < 0.0001), though this effect was not significant beyond that period (sHR 1.38 [0.50–3.83], p = 0.53). Blood loss was also a significant factor in univariate analysis (sHR 1.04 [1.00–1.07], p < 0.039). Regarding the surgical approach, open surgery was independently correlated with an increased risk of recurrence within five years (sHR 4.55 [2.18–9.48], p < 0.0001). Conversely, robotic assistance appears to be associated with a lower risk of recurrence (sHR 0.24 [0.16-0.37], p < 0.0001), including when restricted to laparoscopic procedures (sHR 0.53 [0.29–0.98], p = 0.044).

Among histologic subtypes, clear cell carcinoma (CCC) was associated with higher recurrence risk (sHR 2.13 [1.25–3.62], p = 0.006). Fuhrman grade, analyzed as an ordinal variable, was also predictive: each one-grade increase was associated with a higher risk of recurrence both within 5 years (sHR 2.15 [1.28–3.59], p = 0.004) and beyond (sHR 1.82 [1.24–2.66], p = 0.002).

In contrast to the previously mentioned variables, micropapillary architecture appears to be a protective factor against recurrence (sHR 0.50 [0.27–0.94], p = 0.032).

No statistically significant associations were found for biopsy status, hilar tumor location, ECOG performance status, cystic component, symptoms at diagnosis or tubulopapillary 1 or 2 subtypes.

In the multivariable Fine and Gray model (Table 2), several factors remained independently associated with the risk of local recurrence. The presence of tumor necrosis was a strong predictor (sHR 2.62 [95% CI, 1.54–4.47], p < 0.001), as was a longer delay between diagnosis and surgery (sHR 1.02 [1.003–1.04], p = 0.023). Vascular emboli significantly increased the risk of recurrence within the first five years following diagnosis (sHR 3.90 [1.67–9.08], p = 0.002), as did intraoperative complications during the same time frame (sHR 4.00 [1.65–9.68], p = 0.002).

The complexity of the tumor, as assessed by the RENAL score, was also a significant predictor. Compared to tumors with a low risk, those with an intermediate score had a higher risk of recurrence (sHR 1.70 [1.02–2.85]), and the risk was even greater for tumors with a high score (sHR 2.32 [1.24–4.32]).

Open surgery was correlated with an increased risk of recurrence within five years (sHR 2.25 [1.02–4.97], p = 0.044). Clear cell histology was another independent risk factor (sHR 4.12 [2.18–7.79], p < 0.001).

In contrast, robotic assistance was associated with a significantly lower risk of local recurrence compared to other approaches (sHR 0.50 [0.28–0.88], p = 0.017).

Discussion

In this large multicenter cohort, we evaluated the rate and predictors of local recurrence following nephron-sparing surgery with negative surgical margins (R0) in patients with non-metastatic RCC.

We observed a local recurrence rate of 3.9%, which is consistent with previously reported rates ranging from 0% to 6% [11,12]. While this rate appears low, it remains clinically relevant, particularly considering that all patients had negative margins emphasizing the importance of identifying other risk factors [12].

Our analysis confirmed the independent prognostic value of several adverse pathological features. Tumor characteristic like vascular emboli were associated with local recurrence during five years after surgery. This is in line with prior studies and can be explain if a residual vascular embolus remains in the kidney after NSS, this increase risk of recurrence within the first five years [13]. Conversely, in the absence of residual vascular embolism, there appears to be no significant impact on recurrence, even beyond five years. Necrosis remained a robust predictor in multivariate analysis (HR 2.62), Reflecting the results of Ito et al., who identified necrosis as a major predictor of recurrence even in small T1a tumors [14].

Interestingly, we found no significant association between preoperative biopsy and recurrence. Although isolated cases of tumor seeding have been reported [15,16]. Larger studies—including ours—have not demonstrated an increased recurrence risk following biopsy [17]. These results support the safety of percutaneous biopsy in the preoperative evaluation of renal masses.

We identified intra-operative complications as an independent risk factor for early recurrence (within five years), potentially due to inadvertent tumor spillage or inadequate control of the surgical field in complex cases. This finding is consistent with previous research, such as that by Wood and al, supports this finding, which linked recurrence with increased operative time (175 vs 152 min, $p=0.03$) and blood loss (700 vs 250cc $p>0.01$) [18].

One of the most notable findings of our study is the apparent protective role of robotic assistance. Robotic surgery was correlated with a lower risk of local recurrence, even after adjustment for other prognostic factors. This is in contrast to previous studies, such as that of Peyronnet et al. which found no significant difference in oncologic outcomes between open and laparoscopic approaches [19]. Our results may reflect advantages in precision and tumor handling with robotic platforms, although selection bias (e.g., less complex tumors treated robotically) cannot be excluded.

Tumor location (hilar vs non-hilar) were not associated with recurrence in our cohort. These findings align with those of Sarkis *et al.* who demonstrated that partial nephrectomy remains safe for hilar tumors, with similar functional, and oncological outcomes to those nonhilar tumors [20].

The delay between diagnosis and surgery was independently associated with recurrence risk, albeit with a modest effect size. This result suggests that prolonged time to surgery—potentially reflecting healthcare access limitations or clinical complexity—may negatively impact oncologic outcomes and highlights the importance of timely surgical management.

Another observation from our study is the timing of recurrence. Nearly 70% of local recurrences occurred more than five years after surgery. This contrasts with Speed et al. who reported 83% progression within 5 years and 17% recurrence after 5 years, possibly due to inclusion in our study of new ipsilateral renal lesions [11]. Given that the majority of our cohort would be classified as low-risk according to the UISS criteria, this finding calls into question the adequacy of current follow-up recommendations. While current guidelines typically recommend five years of follow-up for low-risk patients [8]. Our results suggest that extended surveillance may be warranted, even in cases with favorable pathology.

The strengths of our study include its large sample size, multicenter design, and the use of a high-quality prospective database. Importantly, by focusing exclusively on patients with negative margins, we were able to isolate other predictors of recurrence without the confounding influence of positive margins [21].

Some limitations must be acknowledged: The retrospective nature of the analysis may introduce selection bias. Despite prospective data collection, missing data were present, although this was addressed through multiple imputation. Our study also did not account for predisposing conditions such as dialysis or hereditary syndromes, which should be acknowledged as a limitation. Pathologic and imaging data were not centrally reviewed, which may have introduced variability in interpretation. Additionally, although our median follow-up was 66 months, longer-term outcomes remain limited. Some other studies are necessary for more accurate results and better follow-up estimation.

Regarding the number of local recurrent events that occurred during follow-up (n=97) and the number of predictors included in multivariate analysis we cannot excluded risk of overfitting in multivariate model as well as the lack of power to identify independent predictors.

CONCLUSION

In this French multicentre cohort, local recurrence after R0 partial nephrectomy was uncommon but driven by identifiable surgical and pathological factors. Intra-operative complications, treatment delay, tumor complexity, vascular emboli, necrosis and clear-cell histology were correlated with an increased risk of recurrence. Futhermore, our findings support extended surveillance beyond five years, even for seemingly low-risk patients

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Table 1: Patient, surgery and histological characteristics. Data are given as frequency (%) or median (quartiles).

	N=2438
Age at surgery (years), *median [IQR]*	61 [51 - 69]
Sex, n (%)	
Male	1655 (67.9)
Female	783 (32.1)
BMI (kg/m2), median [IQR]	26.7 [23.9 - 30.1]
Smokers, n (%)	487 (20)
Chronic kidney disease, n (%)	85 (3.5)
Surgical approach, n (%)	
MIS	2134 (87.5)
Open surgery	304 (12.5)
Robotic assistance, n (%)	1917 (78.7)
Biopsy, n (%)	458 (18.8)
RENAL score, n (%)	
Low	915 (37.5)
Intermediate	1203 (49.3)
High	320 (13.1)
Delay between diagnosis and surgery (months)	
Mean	3.7 +/- 7.2
Median [IQR]	2 (1.0 ; 4.0)
Intraoperative complication, n (%)	102 (4.2)
Blood loss (ml), median [IQR]	150 (50 ; 300)
Conversion, n (%)	24 (1)
Symptom at diagnosis, n (%)	
Local sign	396 (16.2)
General sign	86 (3.5)
Death (overall), n (%)	61 (2.5)
Tumor size, median [IQR]	3.2 [2.3 - 4.5]
T stage, n (%)	
pT1a	1628 (66.8)
pT1b	494 (20.3)
pT2a	65 (2.7)
pT2b	19 (0.8)
pT3a	232 (9.4)
Histology, n (%)	
CCC	1714 (70.3)
TP1	270 (11.1)
TP2	102 (4.2)
Chromophobe	234 (9.6)
Oncocytoma	13 (0.5)
Others	105 (4.3)
Cystic component, n (%)	473 (19.5)
Necrose content, n (%)	385 (15.8)
Sarcomatoid component, n (%)	60 (2.5)

Vascular embolus, n (%)	116 (4.8)
R0 Margin resection, n (%)	2438 (100)
Fuhrman grade, n (%)	
1	162 (6.6)
2	1293 (53.1)
3	608 (24.9)
4	403 (4.2)
Missing data	272 (11.2)
UISS Score, n (%)	
Low	1333 (54.7)
Intermediate	898 (36.9)
High	208 (8.4)

BMI : Body Mass Index. MIS : minimally invasive surgery. CCC : Clear Cell Carcicoma. TP : Tubulopapillary. UISS : UCLA Integrated Staging System.

Table 2 – Univariate and multivariate results for all predictors of interest for local recurrence.

	Univariate analysis		Multivariate analysis	
Variables	sHR (95% CI)	P value	sHR (95% CI)	P value
Age, year	1.03 (1.01-1.05)	0.004	1.02 (1.001-1.04)	0.042
Necrosis	2.78 (1.84-4.2)	<0.0001	2.62 (1.54-4.47)	<0.001
Delay between diagnosis and surgery, month	1.02 (1.01-1.03)	0.003	1.02 (1.003-1.04)	0.023
Vascular embolus				
0 to 5 years	6.28 (2.68-14.68)	<0.0001	3.90 (1.67-9.08)	0.002
5 to 10 years	1.72 (0.80-3.66)	0.16	1.00 (0.44-2.30)	1.00
Per operative complications				
0 to 5 years	6.58 (2.81-15.42)	<0.0001	4.00 (1.65-9.68)	0.002
5 to 10 years	1.38 (0.50-3.83)	0.53	1.51 (0.55-4.12)	0.42
RENAL score				
Low	ref			
Intermediate	1.85 (1.14-3.01)	0.013	1.70 (1.02-2.85)	0.044
High	2.95 (1.65-5.28)	0.0003	2.32 (1.24-4.32)	0.008
Robotic assistance	0.24 (0.16-0.37)	<0.001	0.50 (0.28-0.88)	0.017
Microcystic architecture	0.50 (0.27-0.94)	0.032	0.49 (0.26-0.94)	0.031
Surgery approach				
MIS, 0 to 5 years	ref			
Open surgery, 0 to 5 years	4.55 (2.18-9.48)	<0.0001	2.25 (1.02-4.97)	0.044
MIS, 5 to 10 years	ref			
Open surgery, 5 to 10 years	0.54 (0.27-1.06)	0.073	0.27 (0.12-0.58)	<0.001
Histology : CCC	2.13 (1.25-3.62)	0.006	4.12 (2.18-7.79)	<0.001
Histology : Chromophobe	5.43 (2.99-9.87)	<0.0001	15.58 (6.81-35.63)	<0.001
Tumor size, cm				
< 4	ref			
Entre 4 et 7	2.41 (1.6-3.65)	<0.0001	1.44 (0.86-2.39)	0.17
>7	2.52 (1.15-5.52)	0.021	2.11 (0.81-5.49)	0.13
Fuhrman grade				
0 to 5 years	2.15 (1.28-3.59)	0.004	-	-
5 to 10 years	1.82 (1.24-2.66)	0.002	-	-
Sarcomatoid component	4.6 (2.19-9.68)	<0.0001	-	-
Blood loss, ml*	1.04 (1.00-1.07)	0.039	-	-
Biopsy before surgery	1.14 (0.7-1.84)	0.61	-	-

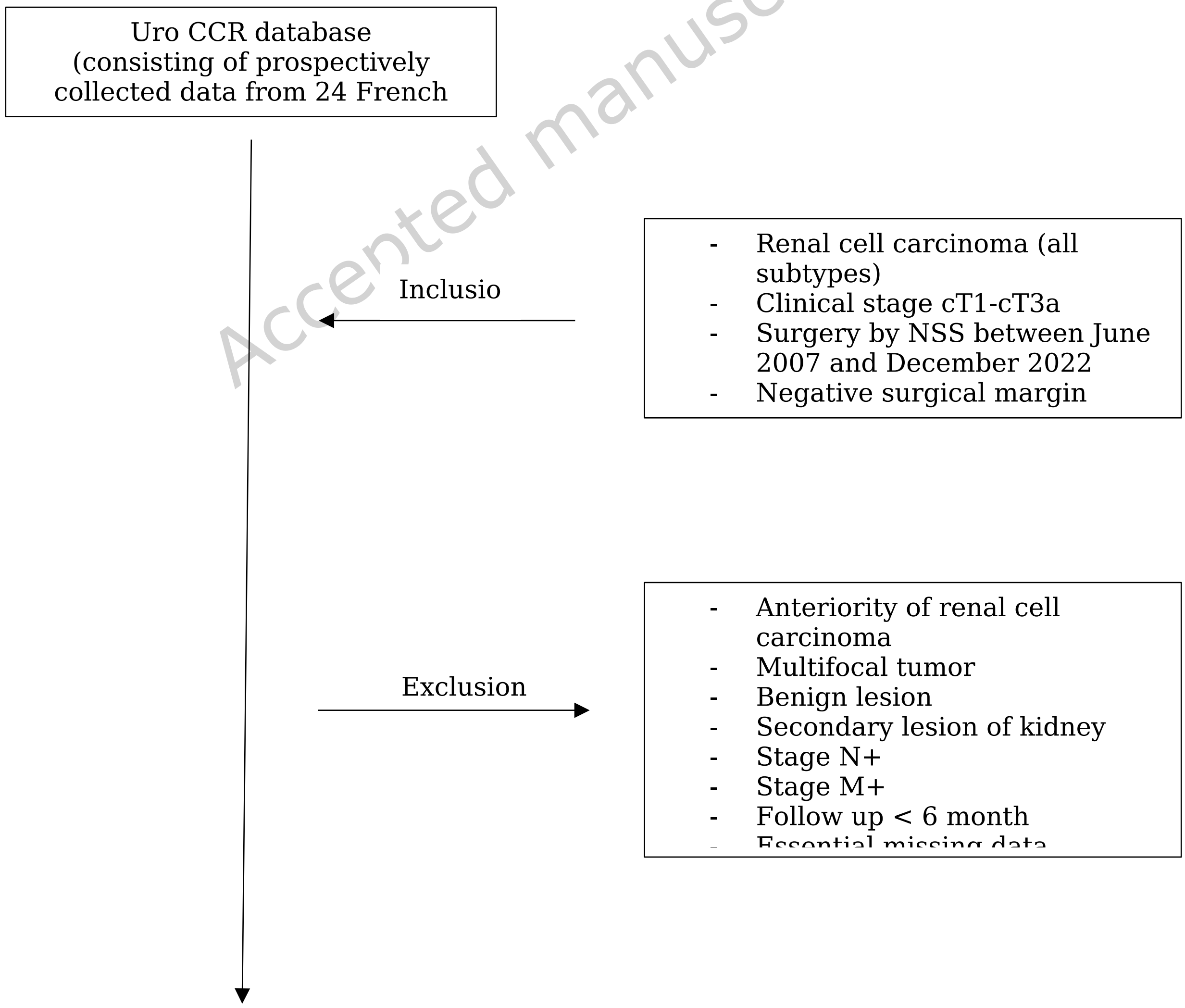
Intra hilar tumor 0 to 5 years 5 to 10 years	0.98 (0.4-2.43) 1.29 (0.73-2.27)	0.97 0.39	- -	- -
ECOG 0, 0 to 5 years 5 to 10 years	ref 1.4 (0.57-3.44)	0.46	-	-
Histology : TP1	0.414 (0.171-1.002)	0.05	-	-
Histology : TP2	1.61 (0.7-3.67)	0.26	-	-

BMI : Body Mass Index. MIS : minimally invasive surgery. CCC : Clear Cell Carcicoma. TP : Tubulopapillary.

* Hazard ratio and their 95% confidence intervals were estimated for the 100 ml increase in blood loss.

** All significant univariate factors were included into a backward selection multivariable Fine and Gray's regression model with tumor size as a forced variable.

Supp Figure 1 – Flowchart demonstrating the inclusion and exclusion criteria for the present study.



Study population
N = 2438

NSS : nephron sparing surgery