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Partial Nephrectomy vs Thermal Ablation for Non-Clear Cell RCC: The UNCLEAR Study (UroCCR 172)

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Research Article

Keywords: Renal cell carcinoma, Non-clear cell renal cell carcinoma, Partial nephrectomy, Thermal ablation, Disease-free survival, Propensity score matching

Posted Date: November 3rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11421886/v1

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Additional Declarations: No competing interests reported.

Abstract

Purpose

To compare disease-free survival (DFS) between partial nephrectomy (PN) and percutaneous ablation (PCA) in patients with non-clear cell renal cell carcinoma (nccRCC), and to identify independent predictors of disease recurrence.

Methods

We performed a retrospective, propensity score-matched analysis of prospectively collected data from the UroCCR registry, including 31 centers (2009–2023). Patients with histologically confirmed cT1a nccRCC treated by PN or PCA were included. Propensity matching (2:1) was based on previous RCC history, tumor size, and histological subtype. DFS was defined as time to first recurrence documented on computed tomography.

Results

After propensity matching, 174 patients were included (PN n = 116; PCA n = 58). Median follow-up was 3.2 years, with 18 recurrences. Five-year DFS was significantly higher after PN than PCA (88.7% vs. 76.8%; HR = 3.11, 95%CI 1.21–8.01; p = 0.018). Previous RCC was the strongest independent predictor of worse DFS in multivariate analysis (HR = 6.23, 95%CI 2.49–15.58; p < 0.01). In univariate exploratory subgroup analyses, the DFS advantage of PN was most pronounced in pRCC (HR = 3.44, 95%CI 1.03–11.46; p = 0.044) and in patients without prior renal malignancy (HR = 6.49; p = 0.005), whereas no statistically significant difference was observed in chRCC. The difference was no longer significant in a post hoc sensitivity analysis restricted to R0 PN and excluding early local recurrences after PCA (HR = 1.85, 95%CI 0.55–6.23; p = 0.32).

Conclusion

In cT1a nccRCC, PN was associated with longer DFS than PCA after propensity matching, particularly in pRCC. Overall survival impact needs prospective evaluation.

Introduction

European and French guidelines recommend partial nephrectomy (PN) as the standard treatment for localized tumors (1, 2). Percutaneous ablation (PCA) is an alternative for selected patients: in a population-based analysis of 4,310 patients with T1a renal cell carcinoma (RCC), 5-year cancer-specific survival was 95% after PCA versus 98% after PN (3). However, a systematic review by the EAU guideline panel of 26 non-randomized studies concluded that the long-term oncological effectiveness of ablation compared with PN remains uncertain, owing to high risk of bias and short follow-up (4).

Non-clear cell RCC (nccRCC) accounts for 20–25% of RCC and clear cell RCC (ccRCC) for approximately 70% (5, 6). Overall, nccRCC carries a more favorable prognosis than ccRCC, with lower recurrence rates across risk groups (7), but outcomes vary widely by subtype: chromophobe RCC (chRCC) is associated with better disease-free survival (DFS), whereas papillary RCC (pRCC) has less favorable outcomes, particularly when high-grade (8), and rare subtypes such as collecting duct carcinoma carry a markedly worse prognosis (9).

Despite this heterogeneity, nccRCC management is not specifically addressed in current guidelines (1, 2). Randomized evidence is lacking: the NEST trial only recently demonstrated the feasibility of randomizing cryoablation against robot-assisted PN in 50 patients (10); the trial is ongoing and its oncological results are not yet available. Retrospective comparisons have reached mixed conclusions. Some report better outcomes with PN (3). In the UroCCR AblatT1b matched-pair analysis of 150 cT1b tumors, local recurrence was significantly higher after thermal ablation than after robot-assisted PN (14.6% vs. 4%; p = 0.02), whereas metastasis rates did not differ and major complications were less frequent after ablation (0% vs. 5.3%) (11). Most studies do not stratify outcomes by histological subtype. In a SEER analysis of 38,155 patients, PN and PCA showed no difference in chRCC for overall survival (HR = 1.68, 95%CI 0.94–3.00; p = 0.078) or cancer-specific survival (HR = 0.34, 95%CI 0.03–3.97; p = 0.389), whereas in pRCC, PN was associated with better overall survival (HR = 1.56, 95%CI 1.18–2.07; p = 0.002) and a trend toward better cancer-specific survival (HR = 2.18, 95%CI 0.99–4.80; p = 0.052) (12). Conversely, in a propensity score-matched analysis of 1,205 patients with stage IA nccRCC from the National Cancer Database, Uhlig et al. found no difference in overall survival between cryoablation and PN in either pRCC (HR = 1.30, 95%CI 0.96–1.75; p = 0.09) or chRCC (HR = 1.38, 95%CI 0.67–2.82; p = 0.38) (13). Overall survival, however, may be insufficiently sensitive to capture differences in local oncological control between modalities.

This study aimed to compare DFS between PN and PCA in patients with nccRCC, and to identify independent predictors of recurrence.

Materials and methods

Study design and population

We performed a retrospective analysis of data prospectively collected in the French national UroCCR registry (NCT03293563), which records all renal tumors regardless of histology or treatment, across 31 centers between 2009 and 2023. UroCCR received institutional review board approval and CNIL authorization (DR-2013-206), and all patients provided written informed consent.

We included patients with a histologically confirmed, non-metastatic nccRCC tumor ≤4 cm (cT1a) treated by PN (open, laparoscopic or robot-assisted) or PCA (cryoablation, radiofrequency or microwave ablation). Patients with unspecified histology, disseminated disease (lymph nodes or metastatic), or follow-up < 3 months were excluded.

Tumor characterization

Histological subtypes were classified according to the WHO classification in use at inclusion (2004, 2016 or 2022) and centrally reviewed by an expert pathologist of the CARARE (CAncers RAres du REin) network. Any tumor without a clear cell component, including mixed subtypes, was eligible. Tumors were grouped as chRCC, pRCC or other, and staged according to the 2017 TNM classification, with size measured on pre-treatment CT or MRI.

Follow-up and endpoints

Follow-up was performed at each center's discretion in accordance with French guidelines, based on the UISS recurrence risk (14). The primary endpoint was DFS, defined as the time from treatment to the first recurrence on CT imaging (local, ipsilateral, contralateral or distant). Patients without recurrence were censored at last follow-up or at 5 years, whichever occurred first; death without recurrence was censored.

Propensity score matching

PN and PCA patients were matched 2:1 on previous RCC, tumor size (≤ 2 cm vs. >2 cm) and histological subtype.

Statistical analysis

Continuous variables are presented as means ± standard deviation and compared with the Welch or Mann-Whitney U test; categorical variables are presented as percentages and compared with the chi-square or Fisher test. Associations of treatment modality, tumor size, histological subtype, previous RCC and baseline renal insufficiency with DFS were assessed by Cox regression; variables with $p < 0.2$ in univariate analysis were entered into the multivariate model. Exploratory subgroup analyses (tumor size, histological subtype, previous RCC) used univariate models only. In a post hoc sensitivity analysis, PN with positive margins and PCA with recurrence at the treated lesion within 12 months were excluded, to account for incomplete primary treatment. Significance was set at $p < 0.05$. Analyses were performed with XLSTAT® 2025.4.1.

Results

Study population

Of 1,057 procedures screened (968 PN, 89 PCA), 269 were excluded (unspecified histology, n = 81; disseminated disease, n = 9; follow-up < 3 months, n = 179), leaving 788 patients (730 PN, 58 PCA) (Online Resource 1).

Propensity score matching was performed using a 2:1 ratio (PN: PCA) based on three matching covariables: previous RCC history, tumor size (defined as ≤2 cm or > 2 cm), and histological subtype

(chRCC, pRCC, or other RCC). The final matched cohort comprised 174 patients: 116 in the PN group and 58 in the PCA group, with no significant difference in baseline characteristics between groups (Table 1).

Table 1
Baseline characteristics of the matched population

Characteristic	PN (n = 116)	PCA (n = 58)	p-value
Patient			
Age, mean (years)	61.3	72.5	< 0.001
BMI, mean (kg/m²)	26.6	27.4	0.590
Sex: male, n (%)	90 (77.6)	43 (74.1)	1.000
ECOG PS 0, n (%)	86 (79.6)	24 (63.2)	0.051
ECOG PS 1, n (%)	17 (15.7)	13 (34.2)	—
ECOG PS 2, n (%)	5 (4.6)	1 (2.6)	—
Comorbidities			
History of cancer, n (%)	19 (16.4)	10 (17.2)	1.000
Renal insufficiency, n (%)	6 (5.2)	6 (10.3)	0.340
Hypertension, n (%)	49 (42.2)	30 (51.7)	0.310
Diabetes, n (%)	16 (13.8)	13 (22.4)	0.220
Dyslipidaemia, n (%)	22 (19.0)	12 (20.7)	0.950
Tobacco use, n (%)	32 (27.6)	22 (37.9)	0.220
Solid tumors, n (%)	**24 (20.7)**	**21 (36.2)**	**0.040**
Familial kidney cancer, n (%)	0 (0.0)	2 (5.3)	0.110
Single kidney, n (%)	5 (4.3)	6 (10.5)	0.210
Tumor			
Side: right, n (%)	65 (56.0)	35 (60.3)	0.700
Size ≤ 2 cm, n (%)	30 (25.9)	18 (31.0)	0.590
Histology: papillary, n (%)	78 (67.2)	39 (67.2)	0.910
Histology: chromophobe, n (%)	28 (24.1)	15 (25.9)	-
Histology: other, n (%)	10 (8.6)	4 (6.9)	-
Surgical margin R0, n (%)	106 (93.0)	-	-
Surgical margin R1, n (%)	5 (4.4)	-	-
Surgical margin R2, n (%)	3 (2.6)	-	-
PN approach: laparoscopy, n (%)	12 (10.3)	-	-

Characteristic	PN (n = 116)	PCA (n = 58)	p-value
PN approach: open surgery, n (%)	24 (20.7)	-	-
PN approach: robotic, n (%)	80 (69)	-	-
PCA modality: cryotherapy, n (%)	-	19 (32.7)	-
PCA modality: microwaves, n (%)	-	1 (1.7)	-
PCA modality: radiofrequency, n (%)	-	38 (65.6)	-
Postoperative outcomes			
Clavien-Dindo grade ≥ 3, n (%)	4 (3.4)	2 (3.4)	1.000

PN, partial nephrectomy; PCA, percutaneous ablation; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status.

p-values from Fisher's exact test or Mann-Whitney U test as appropriate. Bold values: $p < 0.05$.

PCA consisted of radiofrequency (n = 38), cryoablation (n = 19) and microwave ablation (n = 1); PN was robot-assisted (n = 80), laparoscopic (n = 24) or open (n = 12).

PN versus PCA

During a median follow-up of 3.2 years, 18 recurrences occurred. Five-year DFS was 88.7% (95%CI 83.2–92.5) after PN versus 76.8% (95%CI 63.4–86.5) after PCA (Fig. 1). PCA was associated with a higher risk of recurrence in univariate (HR = 2.83, 95%CI 1.13–7.10; p = 0.026) and multivariate analysis (HR = 3.11, 95%CI 1.21–8.01; p = 0.018) (Table 2).

Table 2
Univariate and multivariate analysis for disease-free survival

	Univariate			Multivariate		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Previous cancer	**6.70**	**2.70–16.64**	**< 0.01**	**6.23**	**2.49–15.58**	**< 0.01**
Type of intervention (PCA vs PN)	**2.83**	**1.13–7.10**	**0.026**	**3.11**	**1.21–8.01**	**0.018**
Renal insufficiency	**3.61**	**1.04–12.49**	**0.042**	2.44	0.69–8.63	0.170
Tumor size > 2 cm	0.65	0.27–1.52	0.320	—	—	—
Histology: chromophobe vs papillary	0.89	0.32–2.46	0.670	—	—	—
Histology: other vs papillary	1.54	0.45–5.31	0.330	—	—	—

HR, hazard ratio; CI, confidence interval; PN, partial nephrectomy; PCA, percutaneous ablation.

Multivariate model includes variables with $p < 0.10$ on univariate analysis. Bold values: $p < 0.05$.

Secondary Analysis: Associated Risk Factors

Previous history of malignancy was the strongest independent predictor of recurrence (multivariate HR = 6.23, 95%CI 2.49–15.58; $p < 0.01$). Baseline renal insufficiency was significant in univariate analysis only (HR = 3.61, 95%CI 1.04–12.49; $p = 0.042$; multivariate $p = 0.17$). Tumor size and histological subtype were not associated with DFS (Table 2).

Recurrence patterns

After PN, recurrences (n = 10) were local (n = 2), ipsilateral at a distinct site (n = 1), contralateral (n = 4) or metastatic (n = 3).

After PCA, recurrences (n = 8) were local at the ablation site (n = 5, occurring between 3 and 21 months) or ipsilateral at a distinct site (n = 3); no contralateral or metastatic recurrence was observed.

Subgroup and sensitivity analyses

In subgroup analyses (Table 3), PCA was associated with a higher risk of recurrence in pRCC (n = 117; HR = 3.44, 95%CI 1.03–11.46; $p = 0.044$) (Fig. 2a) and in patients without previous renal cancer (n = 145; HR = 6.49, 95%CI 1.74–24.19; $p = 0.005$) (Fig. 2b).

Table 3
Univariate subgroup analysis for disease-free survival

Variable	N	Events	HR [95% CI]	p-value	DFS 5y PN	DFS 5y PCA
Tumor size						
≤ 2 cm	48	6	3.37 [0.63–17.93]	0.155	86.5%	76.9%
> 2 cm	126	12	3.08 [0.94–10.02]	0.062	89.3%	77.3%
Histology						
Papillary	117	12	**3.44 [1.03–11.46]**	**0.044**	**87.4%**	**80.4%**
Chromophobe	43	4	2.83 [0.39–20.49]	0.302	91.7%	74.7%
Previous cancer						
No	145	10	**6.49 [1.74–24.19]**	**0.005**	**94.5%**	**77.8%**
Yes	29	8	1.23 [0.23–6.42]	0.808	48.4%	77.1%
Negative surgical margin*	160	13	1.85 [0.55–6.23]	0.32	89.0%	84.1%

HR, hazard ratio; CI, confidence interval; DFS, disease-free survival; PN, partial nephrectomy; PCA, percutaneous ablation.

Hazard ratios (HR) and p-values from univariate Cox proportional-hazards models. Bold values: $p < 0.05$.

*Sensitivity analysis restricted to PN patients with negative (R0) margins and to PCA patients without recurrence at the treated site within the first year.

No significant difference was found in chRCC (n = 43; HR = 2.83; p = 0.302) (Fig. 2a), in patients with previous renal cancer (n = 29; HR = 1.23; p = 0.808) (Fig. 2b), or according to tumor size (≤ 2 cm, n = 48: HR = 3.37, p = 0.155; >2 cm, n = 126: HR = 3.08, p = 0.062) (Fig. 2c).

In the sensitivity analysis excluding PN with positive margins and PCA with treated-lesion recurrence within 12 months (106 PN, 54 PCA), the difference was no longer significant (five-year DFS 89.0% vs 84.1%; HR = 1.85, 95%CI 0.55–6.23; p = 0.32) (Fig. 2d).

b Previous cancer history: no previous cancer, HR 6.49 (95% CI 1.74–24.19; p = 0.005); previous cancer, HR 1.23 (95% CI 0.23–6.42; p = 0.808).

c Tumor size: ≤2 cm, HR 3.37 (95% CI 0.63–17.93; p = 0.155); >2 cm, HR 3.08 (95% CI 0.94–10.02; p = 0.062).

d Negative surgical margin (PN R0 vs PCA recurrence-free ≥ 1 year): HR 1.85 (95% CI 0.55–6.23; p = 0.32).

Hazard ratios and p-values are from univariate Cox proportional-hazards models

Discussion

In this propensity score-matched analysis of cT1a nccRCC from the French UroCCR registry, PN was associated with better five-year DFS than PCA (88.7% vs. 76.8%; HR = 3.11, 95%CI 1.21–8.01; p = 0.018). Previous RCC was the strongest independent predictor of recurrence, exceeding the effect of treatment modality. In exploratory subgroup analyses, the advantage of PN was most pronounced in pRCC and in patients without previous RCC.

Previous comparative studies in RCC have reported conflicting results. Talenfeld et al. reported superior cancer-specific survival after PN in T1a RCC (3), and Bianchi et al. found higher five-year DFS after PN in a propensity score-matched analysis (92.8% vs. 80.4%; p = 0.02), with comparable overall survival (15). Conversely, Thompson et al. found no difference in recurrence in an unmatched Kaplan–Meier analysis (16), Yanagisawa et al. reported size-dependent equivalence for cT1a tumors (17), and Xing et al. observed comparable cancer-specific and overall survival after PCA and PN (18). The higher local recurrence rate after PCA has therefore not consistently translated into a survival disadvantage. None of these studies, however, evaluated DFS by nccRCC subtype.

In pRCC, PCA was associated with a higher risk of recurrence (HR = 3.44; p = 0.044), in line with Siev et al., who reported inferior overall survival after ablation in this subtype (HR = 1.53, 95%CI 1.34–1.75) (19), whereas Uhlig et al. found comparable overall survival (13). This discordance may partly reflect endpoint sensitivity, as DFS captures differences in local control that may not yet translate into survival differences. In chRCC, the absence of significant difference, also reported by Uhlig et al. (13), likely reflects the indolent course of this subtype and the limited sample size rather than true equivalence.

Recurrence patterns help interpret these differences. After PCA, most recurrences occurred at the ablation site, consistent with the higher local recurrence rates reported after cryoablation compared with PN in a meta-analysis (OR = 7.83) (20) and after ablation in a Swedish national registry (4.31-fold higher risk) (21). These local recurrences likely reflect, at least partly, primary technical failure, reported in approximately 11% of ablations (22). After PN, contralateral recurrence was the most frequent pattern, a recognized phenomenon in pRCC, which has the highest rate of sporadic multifocality among RCC subtypes (23); metachronous contralateral tumors have been associated with poor prognosis and may reflect hematogenous dissemination (24). The absence of contralateral or metastatic recurrence after PCA most likely reflects the small number of events in this group.

The sensitivity analysis supports this interpretation: after excluding PN with positive margins and early treated-lesion recurrences after PCA, the difference between modalities was no longer significant (HR = 1.85, 95%CI 0.55–6.23; p = 0.32). This agrees with Olweny et al., who reported identical five-year DFS after RFA and PN (89.2% vs. 89.2%; p = 0.78) at a minimum 5-year follow-up (25), and with the meta-analysis by Li et al., restricted to studies with ≥ 5-year follow-up, showing no difference in progression-free survival (HR = 1.26, 95%CI 0.75–2.11) (26). Complete primary ablation may therefore matter more for oncological control than the choice of modality itself.

Previous RCC was the strongest predictor of recurrence (HR = 6.23, 95%CI 2.49–15.58), consistent with the pan-cancer SEER analysis by Zhou et al., in which prior cancer was independently associated with inferior survival in RCC (27). These patients account for approximately 20% of new diagnoses (6), yet remain underrepresented in oncological research.

In both tumor size strata, PCA was associated with a numerically higher risk of recurrence that did not reach significance, possibly owing to limited power. For tumors > 2 cm, Sorce et al. reported higher cancer-specific mortality after local tumor destruction, particularly above 3 cm (28), and preoperative imaging may underestimate stage: in a Swedish national register, 4% of cT1a tumors were upstaged to pT3a (96% of them measuring 2–4 cm), and recurrence was more frequent after ablative techniques than after radical nephrectomy or PN (17.8% vs. 6.8% and 6.0%; p < 0.001) (29). Conversely, the favorable DFS observed for tumors ≤ 2 cm in both groups, together with evidence supporting active surveillance for small renal masses (30), warrants prospective evaluation of deferred intervention in nccRCC.

This study has limitations. First, despite prospective data collection and propensity score matching, residual confounding cannot be excluded, and the marked imbalance before matching (730 PN vs. 58 PCA) suggests selection bias, possibly including under-reporting of ablative procedures. Second, subgroup analyses were limited by small samples and event numbers, particularly in chRCC (n = 43) and tumors ≤ 2 cm (n = 48), and should be considered exploratory. Third, PCA included heterogeneous techniques (radiofrequency 66%, cryoablation 33%, microwave 2%). Fourth, follow-up was left to each center's discretion within national guidelines, which may have affected recurrence detection, and imaging was not centrally reviewed. Finally, metastatic recurrences occurred only after PN (n = 3); although this likely reflects the small PCA sample, the severity of metastatic disease means this finding should not be dismissed.

Conclusion

In this study, PN was associated with significantly longer DFS than PCA in patients with cT1a nccRCC. Treatment modality and previous RCC were both independent predictors of recurrence. The advantage of PN appeared most pronounced in pRCC.

Declarations

Funding Sources

No source of funding.

Disclosure of Interests

All authors declare that they have no conflicts of interests.

Author Contribution

V.C., S.L. and F.T. conceived and designed the study. V.C. performed the statistical analysis and wrote the main manuscript text. J.-C.B., F.A., O.B., K.B., L.B., P.B., R.B., I.B., N.B., E.B., F.B., Vi.C., K.C., C.C., A.C., A.D., S.D.V., N.D., A.F., A.G., M.G., J.G., M.H., E.J., S.L.D., H.L., F.M., C.M., A.M., S.M., C.N., J.O., F.P., Ph.Pa., B.P., J.-J.P., G.P., Ph.Pu., C.R., E.R., R.R.-P., M.R., Cl.S., Ch.S., M.S., L.S., M.V., L.V. and T.W. recruited patients and collected data. V.C. prepared Figures 1–2 and Tables 1–3. S.L. and F.T. supervised the work. All authors reviewed and approved the final manuscript.

Acknowledgement

The authors would like to thank all patients who consented to participate in the UroCCR registry, as well as all urologists and medical staff of the participating centers for their contribution to data collection. The UroCCR database (NCT03293563) received institutional review board approval and obtained authorization from the Commission Nationale de l'Informatique et des Libertés (CNIL, number DR-2013-206). The authors also wish to acknowledge the CARARE (CAncers RAres du REin) network for centralized pathological review.

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Figures

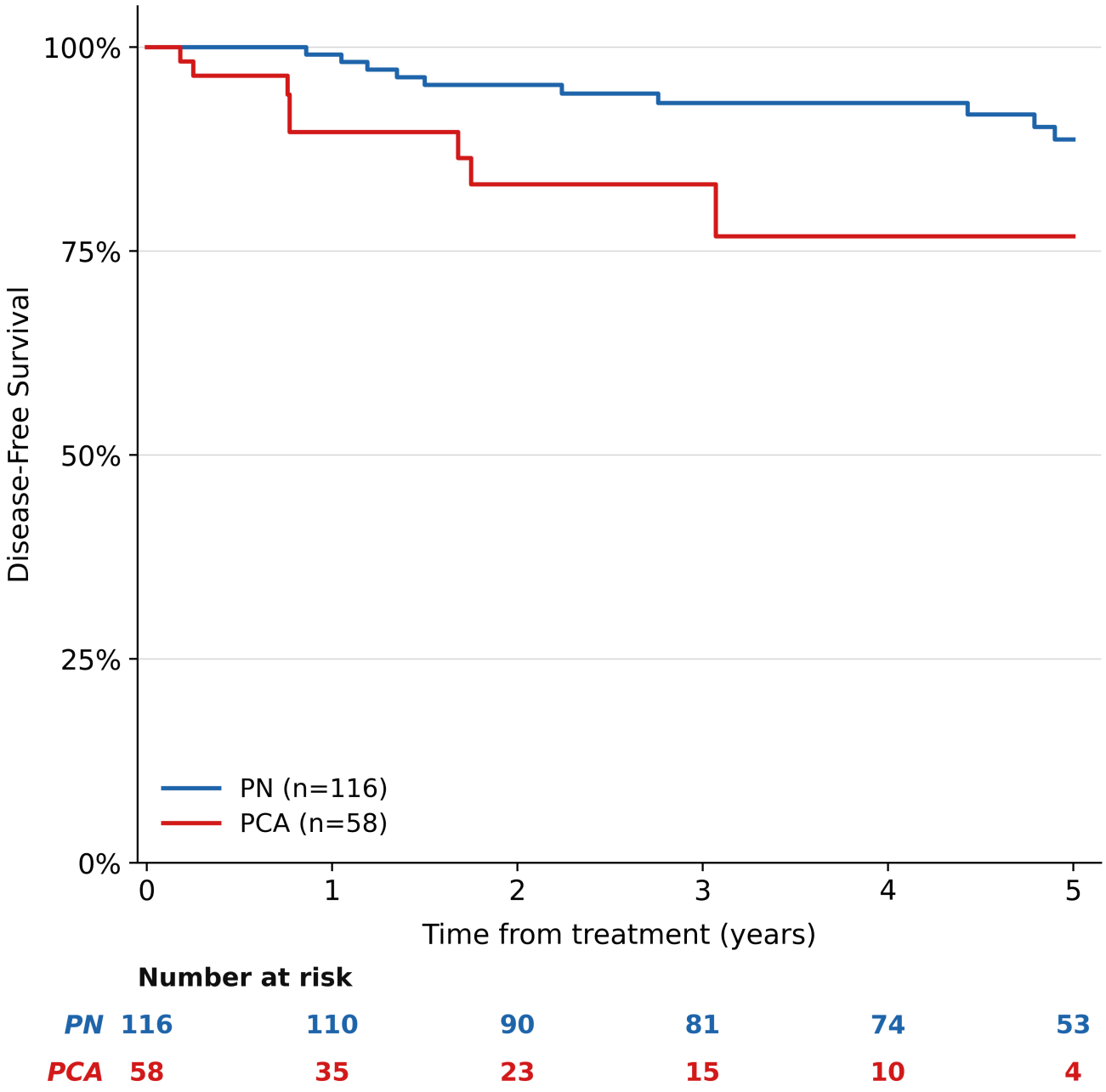


Figure 1

Kaplan-Meier curves comparing DFS between the PN and PCA groups. HR: 3.11; 95% CI: 1.21–8.01; p = 0.018. DFS, disease-free survival; PN, partial nephrectomy; PCA, percutaneous ablation; HR, hazard ratio; CI, confidence interval

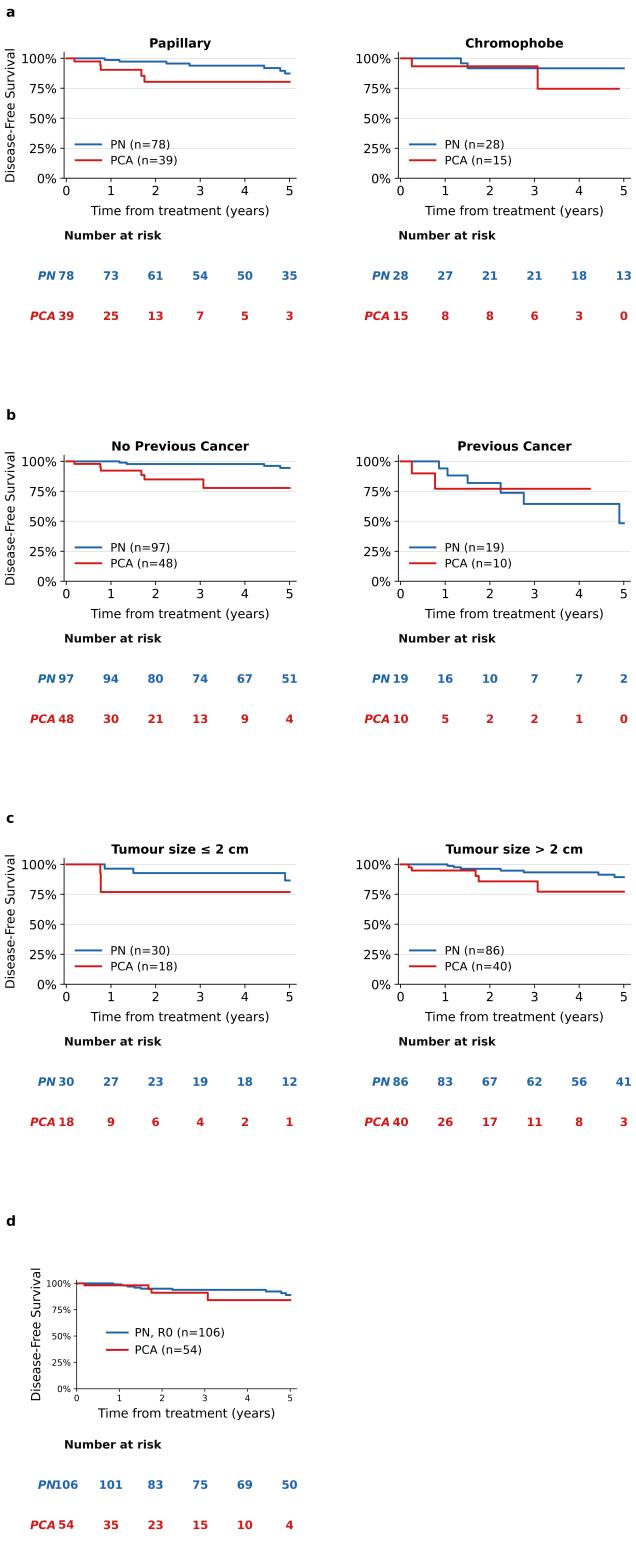


Figure 2

Kaplan-Meier subgroup analyses of disease-free survival: partial nephrectomy (PN) vs percutaneous ablation (PCA). **a**Pathology type: papillary, HR 3.44 (95% CI 1.03–11.46; p = 0.044); chromophobe, HR 2.83 (95% CI 0.39–20.49; p = 0.302).

b Previous cancer history: no previous cancer, HR 6.49 (95% CI 1.74–24.19; p = 0.005); previous cancer, HR 1.23 (95% CI 0.23–6.42; p = 0.808).

c Tumor size: ≤2 cm, HR 3.37 (95% CI 0.63–17.93; p = 0.155); >2 cm, HR 3.08 (95% CI 0.94–10.02; p = 0.062).
d Negative surgical margin (PN R0 vs PCA recurrence-free ≥1 year): HR 1.85 (95% CI 0.55–6.23; p = 0.32).
Hazard ratios and p-values are from univariate Cox proportional-hazards models

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