Supplementary Information

Online Resource 1

Pathological correlates of recurrence timing and post-recurrence survival after surgery for renal cell carcinoma in a multicenter cohort

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Supplementary Table S1 Univariable associations with recurrence at <12 versus ≥12 months

Variable	OR / aOR (95% CI)	P
Age at diagnosis, per year	0.997 (0.970–1.025)	0.8308
Male vs female	1.25 (0.60–2.59)	0.5503
Tumor size, per 10 mm	1.14 (1.03–1.25)	0.0090
Clear-cell vs other histology	0.63 (0.29–1.33)	0.2230
cT ≥3, yes vs no	1.06 (0.57–1.99)	0.8470
pN1 vs pN0/pNx	1.39 (0.58–3.34)	0.4566
High grade, present vs absent	2.09 (1.06–4.14)	0.0337
Tumor necrosis, present vs absent	2.71 (1.49–4.91)	0.0011
Sarcomatoid component, present vs absent	4.73 (1.79–12.47)	0.0017
Rhabdoid component, present vs absent	1.24 (0.30–5.10)	0.7682
Lymphatic invasion, present vs absent	3.10 (1.48–6.52)	0.0028
Venous invasion, present vs absent	1.54 (0.71–3.34)	0.2784
Recorded M1NED vs cM0	2.11 (0.49–9.10)	0.3167

Separate binary logistic models included 187 recurrent patients (84 at <12 and 103 at ≥12 months). ORs, 95% CIs, and P values are Wald-based. These analyses describe timing conditional on observed recurrence, not recurrence risk in all surgical patients. High grade follows the highest-recorded-grade rule. No multiplicity adjustment was applied.

Supplementary Table S2 Exploratory three-group recurrence-timing analyses

a Multivariable three-group model

Variable	<6 vs ≥12 months aOR (95% CI)	P	6 to <12 vs ≥12 months aOR (95% CI)	P	Overall P
Tumor size, per 10 mm	1.09 (0.96–1.24)	0.1756	1.02 (0.88–1.17)	0.7935	0.3901
High grade, present vs absent	1.21 (0.50–3.03)	0.6709	2.31 (0.83–7.52)	0.1293	0.2817
Tumor necrosis, present vs absent	2.08 (0.93–4.67)	0.0740	2.88 (1.25–6.85)	0.0139	0.0252
Lymphatic invasion, present vs absent	4.49 (1.82–11.55)	0.0013	1.63 (0.51–4.93)	0.3946	0.0046
cT ≥3, yes vs no	0.80 (0.35–1.88)	0.6031	0.72 (0.30–1.75)	0.4633	0.7292
pN1 vs pN0/pNx	0.93 (0.28–2.93)	0.9071	1.20 (0.32–4.09)	0.7735	0.9339

The exploratory six-covariate multinomial model included all 187 recurrent patients (47 at <6, 37 at 6 to <12, and 103 at ≥ 12 months). The ≥ 12-month group was the reference. All six covariates were entered simultaneously. CIs are profile-likelihood intervals; contrast P values are Wald tests, and overall P values are likelihood-ratio tests with 2 degrees of freedom. This three-group model was used as an additional exploratory analysis alongside the main binary analysis. No multiplicity adjustment was applied.

Supplementary Table S2 continued

b Univariable multinomial models

Variable	<6 vs ≥12 OR (95% CI)	P	6 to <12 vs ≥12 OR (95% CI)	P	Overall P
Age at diagnosis, per year	1.003 (0.970–1.038)	0.8488	0.989 (0.954–1.025)	0.5550	0.7832
Male vs female	1.15 (0.48–2.73)	0.7566	1.40 (0.52–3.79)	0.5037	0.7860
Tumor size, per 10 mm	1.17 (1.05–1.31)	0.0052	1.09 (0.96–1.23)	0.1685	0.0147
Clear-cell vs other histology	0.56 (0.23–1.33)	0.1882	0.73 (0.27–1.96)	0.5334	0.4185
cT ≥3, yes vs no	1.18 (0.55–2.53)	0.6728	0.94 (0.42–2.10)	0.8781	0.8771
pN1 vs pN0/pNx	1.46 (0.53–4.05)	0.4632	1.31 (0.42–4.05)	0.6429	0.7456
High grade, present vs absent	1.61 (0.73–3.55)	0.2360	3.15 (1.13–8.82)	0.0286	0.0486
Tumor necrosis, present vs absent	2.31 (1.14–4.67)	0.0202	3.33 (1.53–7.28)	0.0025	0.0029
Sarcomatoid component, present vs absent	5.54 (1.93–15.89)	0.0014	3.77 (1.18–12.09)	0.0255	0.0024
Rhabdoid component, present vs absent	0.54 (0.06–4.95)	0.5841	2.18 (0.46–10.26)	0.3223	0.4175
Lymphatic invasion, present vs absent	4.70 (2.06–10.70)	0.0002	1.62 (0.59–4.42)	0.3508	0.0009
Venous invasion, present vs absent	1.46 (0.57–3.73)	0.4249	1.64 (0.57–4.72)	0.3597	0.5395
Recorded M1NED vs cM0	0.72 (0.07–7.16)	0.7828	4.04 (0.86–18.99)	0.0770	0.1406

Separate models included 187 recurrent patients. ORs and CIs are Wald-based. Contrast P values are Wald tests; overall P values are likelihood-ratio tests with 2 degrees of freedom. No multiplicity adjustment was applied. M1NED, metastatic disease recorded as no evidence of disease.

Supplementary Table S3 Direct comparison of the first-year recurrence intervals

Variable	OR / aOR (95% CI)	P
Tumor size, per 10 mm	1.07 (0.92–1.24)	0.3762
High grade, present vs absent	0.53 (0.15–1.80)	0.3063
Tumor necrosis, present vs absent	0.72 (0.27–1.88)	0.5028
Lymphatic invasion, present vs absent	2.76 (0.91–8.37)	0.0731
cT ≥3, yes vs no	1.11 (0.41–3.02)	0.8395
pN1 vs pN0/pNx	0.78 (0.20–3.07)	0.7167

The outcome contrast is <6 versus 6 to <12 months. Estimates use coefficient vectors and the full covariance matrix from the exploratory six-covariate multinomial model in 187 patients, not a model fitted only to the 84 first-year recurrences. CIs and P values are Wald-based. Inconclusive contrasts do not establish equivalence.

Supplementary Table S4 Sensitivity analyses of the binary recurrence-timing model

a Restricted to cM0

Variable	OR / aOR (95% CI)	P
Tumor size, per 10 mm	1.04 (0.93–1.16)	0.5166
High grade, present vs absent	1.54 (0.72–3.29)	0.2671
Tumor necrosis, present vs absent	2.68 (1.34–5.36)	0.0052
Lymphatic invasion, present vs absent	3.42 (1.44–8.10)	0.0053
cT ≥3, yes vs no	0.74 (0.36–1.51)	0.4060
pN1 vs pN0/pNx	1.25 (0.45–3.46)	0.6730

The model retained all six covariates in 179 recurrent cM0 patients (79 at <12 and 100 at ≥12 months). CIs and P values in all panels of Supplementary Table S4 are Wald-based.

Supplementary Table S4 continued

b Additional adjustment for recorded M1NED

Variable	OR / aOR (95% CI)	P
Tumor size, per 10 mm	1.06 (0.95–1.18)	0.3200
High grade, present vs absent	1.55 (0.73–3.30)	0.2559
Tumor necrosis, present vs absent	2.40 (1.23–4.67)	0.0101
Lymphatic invasion, present vs absent	3.12 (1.35–7.21)	0.0077
cT ≥3, yes vs no	0.76 (0.38–1.52)	0.4425
pN1 vs pN0/pNx	1.04 (0.38–2.83)	0.9419
Recorded M1NED vs cM0	1.44 (0.30–6.84)	0.6433

All 187 recurrent patients were included. Recorded M1NED status was added to the six covariates. Only eight recurrent patients were registered as M1NED; the estimate for this category is imprecise and does not establish an M1NED-specific effect.

c Restricted to clear-cell RCC

Variable	OR / aOR (95% CI)	P
Tumor size, per 10 mm	1.02 (0.90–1.16)	0.7361
High grade, present vs absent	1.59 (0.72–3.53)	0.2552
Tumor necrosis, present vs absent	2.18 (1.04–4.59)	0.0400
Lymphatic invasion, present vs absent	2.21 (0.83–5.87)	0.1116
cT ≥3, yes vs no	0.62 (0.29–1.32)	0.2147
pN1 vs pN0/pNx	0.86 (0.25–3.00)	0.8093

The model retained all six covariates in 154 recurrent clear-cell cases (66 at <12 and 88 at ≥12 months). The lymphatic-invasion estimate was less precise and its CI included 1. No histology interaction was established.

Supplementary Table S5 Survival sensitivity analyses

a cM0 restriction and clear-cell restriction

Population / covariate	HR (95% CI)	P
cM0: recurrence <12 vs ≥12 months	2.01 (1.27–3.16)	0.0027
Clear-cell: recurrence <12 vs ≥12 months	1.52 (0.94–2.47)	0.0858
Clear-cell: age at diagnosis, per year	1.034 (1.007–1.062)	0.0133
Clear-cell: tumor necrosis	1.44 (0.89–2.32)	0.1392

The cM0 model included 179 patients and 84 deaths and adjusted for age and necrosis. The clear-cell model included 154 patients and 71 deaths. Both populations included one patient censored at time zero. CIs and P values throughout Supplementary Table S5 are Wald-based; ties used the Breslow method.

b Additional M1NED adjustment

Variable	HR (95% CI)	P
Recurrence <12 vs ≥12 months	1.89 (1.21–2.97)	0.0056
Age at diagnosis, per year	1.023 (1.001–1.045)	0.0411
Tumor necrosis	1.31 (0.84–2.05)	0.2272
Recorded M1NED vs cM0	0.40 (0.10–1.65)	0.2041

All 187 recurrent patients and 86 deaths were included, with one patient censored at time zero. The model added recorded M1NED status to recurrence timing, age, and necrosis. Exact complete-resection and NED dates were unavailable; renal surgery was the common time origin. These data do not establish an M1NED-specific survival association.

Supplementary Table S5 continued

c Models with and without bone-metastasis adjustment

Adjustment	Variable	HR (95% CI)	P
Age + necrosis	Recurrence <12 vs ≥12 months	1.60 (0.99–2.59)	0.0564
Age + necrosis	Age at diagnosis, per year	1.023 (1.000–1.046)	0.0500
Age + necrosis	Tumor necrosis	1.36 (0.84–2.19)	0.2085
Age + necrosis + bone	Recurrence <12 vs ≥12 months	1.47 (0.91–2.39)	0.1140
Age + necrosis + bone	Age at diagnosis, per year	1.026 (1.003–1.048)	0.0256
Age + necrosis + bone	Tumor necrosis	1.53 (0.94–2.49)	0.0903
Age + necrosis + bone	Bone metastasis	1.85 (1.03–3.33)	0.0394

Both models included the same 161 patients and 77 deaths, including one censored on the recurrence date. Recurrence location was undocumented in 26 of 187 patients; these records were treated as missing, not as absence of metastasis. The recurrence-timing association was not statistically significant in either model. The same-sample comparison separates the effect of adding bone metastasis from the effect of restricting the sample. Neither model adjusts for total metastatic burden, and selection due to missing site information remains possible.

Bone metastasis was included as a focused sensitivity covariate because of its reported adverse prognostic association: McKay RR, Kroeger N, Xie W et al (2014) Impact of bone and liver metastases on patients with renal cell carcinoma treated with targeted therapy. Eur Urol 65:577–584. https://doi.org/10.1016/j.eururo.2013.08.012

Supplementary Table S6 Sensitivity analyses of the exploratory multinomial model

a Restricted to cM0

Variable	<6 vs ≥12 months aOR (95% CI)	P	6 to <12 vs ≥12 months aOR (95% CI)	P
Tumor size, per 10 mm	1.07 (0.94–1.22)	0.3112	0.99 (0.86–1.15)	0.9242
High grade, present vs absent	1.28 (0.52–3.12)	0.5897	2.06 (0.69–6.16)	0.1966
Tumor necrosis, present vs absent	2.16 (0.95–4.92)	0.0660	3.57 (1.45–8.80)	0.0057
Lymphatic invasion, present vs absent	4.92 (1.93–12.54)	0.0008	1.62 (0.49–5.33)	0.4306
cT ≥3, yes vs no	0.78 (0.33–1.83)	0.5703	0.69 (0.28–1.73)	0.4322
pN1 vs pN0/pNx	1.05 (0.32–3.43)	0.9388	1.59 (0.44–5.77)	0.4784

All six covariates were retained in 179 recurrent cM0 patients (46 at <6, 33 at 6 to <12, and 100 at ≥12 months). All CIs and contrast P values in Supplementary Table S6 are Wald-based.

b Additional adjustment for recorded M1NED

Variable	<6 vs ≥12 months aOR (95% CI)	P	6 to <12 vs ≥12 months aOR (95% CI)	P
Tumor size, per 10 mm	1.09 (0.96–1.24)	0.1643	1.01 (0.87–1.16)	0.9343
High grade, present vs absent	1.25 (0.51–3.05)	0.6268	2.16 (0.73–6.42)	0.1653
Tumor necrosis, present vs absent	2.07 (0.93–4.63)	0.0754	2.86 (1.23–6.69)	0.0150
Lymphatic invasion, present vs absent	4.46 (1.78–11.19)	0.0014	1.62 (0.52–5.01)	0.4065
cT ≥3, yes vs no	0.80 (0.35–1.85)	0.6024	0.73 (0.31–1.77)	0.4920
pN1 vs pN0/pNx	0.95 (0.30–3.05)	0.9312	1.19 (0.33–4.25)	0.7932
Recorded M1NED vs cM0	0.48 (0.04–5.11)	0.5406	2.81 (0.54–14.50)	0.2172

All 187 recurrent patients were included. The model retained the six covariates plus recorded M1NED status. The eight recurrent M1NED cases were distributed as 1, 4, and 3 across the three intervals, respectively; category-specific estimates are imprecise.

Supplementary Table S6 continued

c Restricted to clear-cell RCC

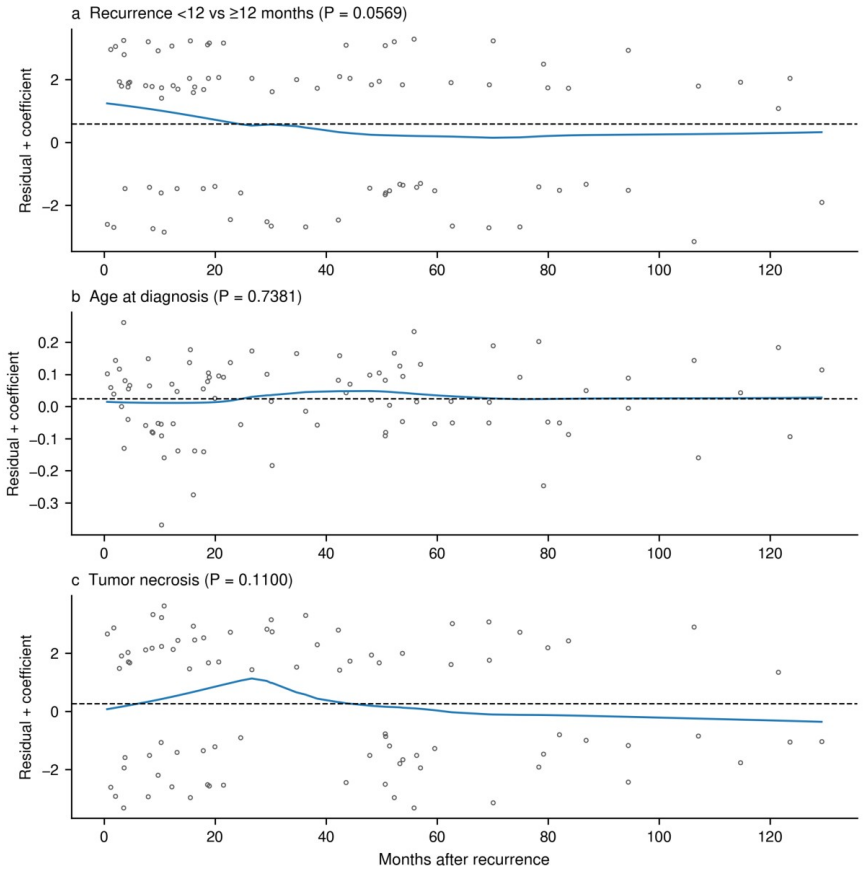
Variable	<6 vs ≥12 months aOR (95% CI)	P	6 to <12 vs ≥12 months aOR (95% CI)	P
Tumor size, per 10 mm	1.09 (0.94–1.26)	0.2497	0.92 (0.78–1.10)	0.3787
High grade, present vs absent	1.09 (0.43–2.75)	0.8632	3.03 (0.89–10.24)	0.0749
Tumor necrosis, present vs absent	1.63 (0.66–4.03)	0.2912	3.21 (1.19–8.66)	0.0211
Lymphatic invasion, present vs absent	2.63 (0.88–7.87)	0.0835	1.62 (0.44–5.96)	0.4647
cT ≥3, yes vs no	0.72 (0.29–1.79)	0.4838	0.53 (0.20–1.39)	0.1986
pN1 vs pN0/pNx	0.50 (0.09–2.85)	0.4345	1.31 (0.30–5.66)	0.7173

All six covariates were retained in 154 recurrent clear-cell cases (36 at <6, 30 at 6 to <12, and 88 at ≥12 months). No histology interaction was established.

Estimation notes

Recurrence intervals use calendar-month anniversaries. High grade is the highest recorded numerical grade ≥ 3 across the recorded grading systems. Survival durations use 30.4375 days/month. Kaplan–Meier CIs use Greenwood variance on a log–log scale; median CIs are obtained by inversion at survival=0.5. Follow-up uses reverse Kaplan–Meier estimation. No multiplicity adjustment was applied. Calculations used Python 3.12.14, NumPy 2.3.5, and SciPy 1.17.0. All survival intervals were calculated from recorded dates. One patient was censored at time zero and contributed no positive follow-up. The exploratory three-group multivariable results in Supplementary Table S2a use profile-likelihood CIs; all other supplementary logistic CIs use the Wald method.

Supplementary Fig. S1 Cox proportional-hazards diagnostics



a–c Primary Cox model (187 patients, 86 deaths; one censored at time zero): scaled Schoenfeld residuals plus the fitted coefficient. Solid curves are descriptive local linear LOWESS smoothers (fraction 0.65, without robustness iterations); dashed lines show fitted constant coefficients. Panels show recurrence timing, diagnostic age, and necrosis. The score-test transformation was 1 − S_KM(t−), centered across event times. Time is measured from recurrence.

Model	Patients	Deaths	Global P	Timing-term P
Primary	187	86	0.1562	0.0569
Additional lymphatic adjustment	187	86	0.1530	0.0460
Documented-site bone adjustment	161	77	0.4675	0.1716

The primary global score test yielded χ^2=5.223 (3 df; P=0.1562). Non-significant tests do not prove proportional hazards. The timing smoother suggests attenuation over follow-up, and the timing-term test in the model additionally adjusted for lymphatic invasion yielded P=0.0460. Constant HRs therefore summarize an association that may change over time. Sparse late risk sets limit interpretation. The direct exploratory log-rank comparison of the first-year groups included 84 patients and 52 deaths (χ^2=0.641; P=0.4234) and does not establish equivalence.

Methods reference: Grambsch PM, Therneau TM (1994) Biometrika 81:515–526. https://doi.org/10.1093/biomet/81.3.515 (manuscript reference [14]).