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

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Abstract

Background

We examined the associations of pathological findings with recurrence within 1 year after surgery for renal cell carcinoma and the association between recurrence timing and subsequent survival.

Methods

This retrospective study included 478 patients from seven Japanese centers: 467 without distant metastasis and 11 with resected metastatic disease recorded as no evidence of disease. Among recurrent patients, binary logistic regression compared recurrence at < 12 versus ≥ 12 months from renal surgery, adjusting for tumor size, grade, necrosis, lymphatic invasion, clinical T category, and pathological nodal status. Three-group analyses using a 6-month subdivision were exploratory. Kaplan–Meier analysis and Cox regression assessed post-recurrence overall survival.

Results

Recurrence occurred in 187 patients: 84 at < 12 months and 103 at ≥ 12 months. Tumor necrosis (adjusted odds ratio 2.40, 95% confidence interval 1.24–4.72; P = 0.0099) and lymphatic invasion (3.12, 1.38–7.42; P = 0.0077) were associated with recurrence at < 12 months. Among recurrent patients, 86 died. Median post-recurrence survival was 50.6 versus 82.0 months for recurrence at < 12 versus ≥ 12 months. The mortality hazard ratio adjusted for age and necrosis was 1.81 (95% confidence interval 1.15–2.84; P = 0.0098).

Conclusions

Among patients who recurred, tumor necrosis and lymphatic invasion were associated with recurrence within 1 year, which was associated with poorer subsequent survival. These exploratory findings require external validation before informing clinical management.

Introduction

Postoperative recurrence remains a major concern in renal cell carcinoma (RCC) [1]. Established prognostic models incorporate stage, tumor size, grade, nodal involvement, and necrosis [2–4], and pooled studies support the prognostic relevance of these features [5]. However, less is known about the associations of pathological findings with recurrence during the first postoperative year among patients who subsequently recur.

The benefits of adjuvant pembrolizumab in selected patients with clear-cell RCC have increased interest in postoperative risk assessment [6, 7]. However, an association with recurrence does not necessarily indicate benefit from a particular treatment. Shorter recurrence intervals have been associated with worse survival, although studies have used different endpoints and thresholds [8–11]. Adverse pathological features have also been linked to recurrence within 1 year [12]. We therefore examined pathological correlates of recurrence at < 12 versus ≥ 12 months and the relationship between recurrence timing and post-recurrence overall survival (PR-OS). The 1-year threshold was supported by previous studies [8, 12]. We additionally performed an exploratory three-group analysis (< 6, 6 to < 12, and ≥ 12 months) to examine pathological associations with recurrence timing within the first postoperative year in greater detail.

Patients and Methods

Study design and population

This exploratory analysis used a multicenter retrospective cohort coordinated by the Department of Urology, Hokkaido University Hospital. Seven Japanese centers contributed cases: Nagasaki University, Chiba University, Akita University, Sapporo City General Hospital, Hokkaido University Hospital, Hokkaido Cancer Center, and Yamagata University. The parent protocol targeted adults aged ≥ 18 years who underwent surgery from January 2010 through December 2021 and who had pT2 grade 4 or sarcomatoid tumors with N0M0 disease; pT3–4 tumors of any grade with N0M0 disease; any pT category with N1M0 disease; or complete resection of the primary tumor and metastases at nephrectomy or within 1 year thereafter. Both clear-cell and non-clear-cell cancers were included. These stage and pathological risk criteria were adapted from KEYNOTE-564 [6], without requiring all trial eligibility criteria. Investigators selected 515 of 559 submitted cases. The exclusion of 23 patients receiving preoperative systemic tumor-reducing therapy and 14 with insufficient data left 478 available cases. Follow-up was based on recorded dates of last clinical contact. Clinical data were coded using study identifiers and transferred to the coordinating center for data management.

The primary analysis included 467 patients with clinically nonmetastatic (cM0) disease and 11 with clinical M1 disease registered as M1 no evidence of disease (M1NED). M1NED denotes metastatic disease rendered free of detectable disease post-resection. Classification was based on the recorded category and investigator clarification that no residual disease was present and that the eight subsequent events represented new recurrences after NED. The exact dates of complete resection of the primary tumor and metastases and of NED attainment were unavailable. Thus, we used the recorded renal surgery date as the common analysis origin without assuming that it was the actual NED date. Analyses restricted to cM0 disease assessed the influence of including M1NED.

Variable definitions and follow-up

Clinical and pathological variables included age at diagnosis, sex, tumor diameter, histology, clinical T (cT) category, pathological nodal (pN) status, grade, and invasion features. High grade was defined as the highest recorded numerical grade ≥ 3 across World Health Organization/International Society of Urological Pathology, Fuhrman, and Japanese reporting systems; these systems were not considered interchangeable. Lymphatic invasion was recorded separately from venous invasion and combined lymphovascular invasion. pN1 was compared with pN0/pNx, without assuming that pNx indicated node negativity. Sarcomatoid and rhabdoid components were recorded separately.

The main recurrence-timing comparison was < 12 versus ≥ 12 months from the recorded renal surgery date. An exploratory analysis subdivided first-year recurrence into < 6 and 6 to < 12 months. Intervals used calendar-month anniversaries, with events on a boundary entering the later interval. For M1NED, these intervals represent time from renal surgery, not verified intervals from attainment of NED. Follow-up imaging followed routine practice at each center and varied with recurrence risk and clinical judgment.

PR-OS was measured from first recurrence to death from any cause or the last documented date alive. Durations were calculated directly from recorded dates. One patient whose recurrence and last-contact dates were identical was censored on the recurrence date (time zero). Median follow-up from surgery was estimated by reverse Kaplan–Meier analysis [13].

Recurrence location was undocumented in 26 of 187 recurrent patients. These records were treated as missing, rather than as the absence of metastatic disease. Recurrence-site count was therefore omitted from the primary Cox model.

Statistical analysis

Continuous variables are presented as medians and interquartile ranges, with comparisons using Kruskal–Wallis tests. Comparisons of categorical variables used Pearson chi-square or Fisher–Freeman–Halton exact tests, as specified in Table 1. The study size was determined by the available cohort. Patients without documented recurrence contributed to descriptive comparisons but not to regression analyses of recurrence timing. No values were missing for the variables in Table 1 or the primary regression models; no imputation was performed.

Table 1
Clinicopathological characteristics by recurrence interval

Characteristic	No documented recurrence (n = 291)	< 6 months (n = 47)	6 to < 12 months (n = 37)	≥ 12 months (n = 103)	P
Age at diagnosis, years	70 (61–77)	68 (59–77)	67 (57.5–73.5)	67 (60–74)	0.213
Male sex	205 (70.4)	38 (80.9)	31 (83.8)	81 (78.6)	0.108
Tumor size, mm	54 (40–78)	89 (70–110)	75 (63.5–101.5)	74 (50–93)	< 0.001
Clear-cell histology	258 (88.7)	36 (76.6)	30 (81.1)	88 (85.4)	0.112
cT ≥ 3	142 (48.8)	34 (72.3)	25 (67.6)	71 (68.9)	< 0.001
pN1	8 (2.7)	7 (14.9)	5 (13.5)	11 (10.7)	< 0.001
High grade	125 (43.0)	36 (76.6)	32 (86.5)	69 (67.0)	< 0.001
Tumor necrosis	59 (20.3)	25 (53.2)	23 (62.2)	34 (33.0)	< 0.001
Sarcomatoid component	16 (5.5)	12 (25.5)	7 (18.9)	6 (5.8)	< 0.001
Rhabdoid component	9 (3.1)	1 (2.1)	3 (8.1)	4 (3.9)	0.418
Lymphatic invasion	32 (11.0)	19 (40.4)	7 (18.9)	13 (12.6)	< 0.001
Venous invasion	219 (75.3)	40 (85.1)	32 (86.5)	82 (79.6)	0.224
Recorded M1NED	3 (1.0)	1 (2.1)	4 (10.8)	3 (2.9)	0.008

Values are presented as median (interquartile range) or n (%). P values indicate comparisons among all four groups. Continuous variables: Kruskal–Wallis test; pN1, sarcomatoid component, rhabdoid component, and recorded M1NED: Fisher–Freeman–Halton exact test. Other categorical variables: Pearson chi-square test. High grade is the highest recorded numerical grade ≥ 3. pN1 is compared with pN0/pNx; pNx does not imply node negativity. M1NED denotes the recorded classification supported by investigator clarification of no residual disease. Exact complete-resection and NED dates were unavailable; the recorded renal surgery date was used as the time origin. There were no missing values for the displayed variables.

For the main multivariable analysis of recurrence timing, binary logistic regression compared recurrence at < 12 versus ≥ 12 months among 187 recurrent patients, with ≥ 12 months as the reference. The multivariable model simultaneously included tumor diameter, high grade, necrosis, lymphatic invasion, cT ≥ 3, and pN1 to account for tumor burden, differentiation, and invasion. These six covariates required six slope coefficients. Univariable models evaluated each factor separately; variable inclusion was not based on statistical significance. Odds ratios (ORs), adjusted ORs (aORs), and 95% confidence intervals (CIs) are reported. CIs for the main multivariable model were obtained by profile likelihood, and P values by two-sided Wald tests. Univariable and binary sensitivity-model CIs were Wald-based. Additional

exploratory three-group analyses used multinomial logistic regression to compare < 6 and 6 to < 12 months with ≥ 12 months, including the same six covariates. These models required 12 slope coefficients; direct first-year contrasts used their full covariance matrix. Details are provided in Online Resource 1. All recurrence-timing estimates are conditional on observed recurrence and do not estimate recurrence risk in the full surgical cohort.

PR-OS was estimated using Kaplan–Meier analysis and compared using log-rank tests, including a direct exploratory comparison of the two first-year recurrence intervals. Univariable Cox regression evaluated recurrence at < 12 versus ≥ 12 months, diagnostic age, necrosis, and lymphatic invasion. The primary multivariable model included recurrence timing, age at diagnosis, and tumor necrosis. Age addressed differences relevant to all-cause mortality; necrosis was included as an established adverse primary-tumor feature [3] associated with first-year recurrence [12]. An expanded model added lymphatic invasion to assess the recurrence-timing association after adjustment for this pathological feature. The primary and expanded models contained three and four covariates, respectively, with 86 deaths. Cox models used Breslow handling of tied event times and Wald CIs. Proportional hazards were assessed using time-interaction score tests and scaled Schoenfeld residual plots [14].

Sensitivity analyses restricted the cohort to cM0 or clear-cell RCC and additionally adjusted for recorded M1NED status. Additional analyses and proportional-hazards diagnostics are provided in Online Resource 1.

Automatic variable selection was not used. All tests were two-sided, without multiplicity adjustment, and findings were interpreted as exploratory. Analyses used JMP Pro 18.0 and Python 3.12.14 with NumPy 2.3.5 and SciPy 1.17.0. Logistic models were fitted by maximum likelihood and Cox models by partial likelihood.

Results

Cohort and descriptive findings

The primary cohort comprised 478 patients: 467 with cM0 disease and 11 registered as M1NED (Fig. 1). Recurrence was documented in 187 patients, including eight registered as M1NED; 291 patients had no documented recurrence. Recurrence occurred at < 12 months in 84 patients and at ≥ 12 months in 103. Of the 84 first-year recurrences, 47 occurred at < 6 months and 37 at 6 to < 12 months. The cohort included 412 and 66 cases of clear-cell and non-clear-cell cancers, respectively. The median follow-up was 66.0 months (95% CI 59.7–71.4) among all 478 patients.

Among patients with recurrence at < 12 versus ≥ 12 months, lymphatic invasion was present in 26/84 (31.0%) versus 13/103 (12.6%), and necrosis in 48/84 (57.1%) versus 34/103 (33.0%). Table 1 presents the 6-month subdivision for descriptive context and also includes patients without documented recurrence.

Pathological findings and recurrence timing

In univariable binary logistic analyses, larger tumor diameter, high grade, necrosis, a sarcomatoid component, and lymphatic invasion were associated with recurrence at < 12 versus ≥ 12 months. All univariable estimates are presented in Online Resource 1 (Supplementary Table S1).

After simultaneous adjustment for all six covariates, tumor necrosis (aOR 2.40, 95% CI 1.24–4.72; P = 0.0099) and lymphatic invasion (aOR 3.12, 95% CI 1.38–7.42; P = 0.0077) were associated with recurrence at < 12 versus ≥ 12 months (Table 2). The other covariates were not statistically significant.

Table 2
Multivariable associations with recurrence at < 12 versus ≥ 12 months

Variable	aOR (95% CI)	P
Tumor size, per 10 mm	1.06 (0.95–1.18)	0.2922
High grade, present vs absent	1.58 (0.75–3.40)	0.2349
Tumor necrosis, present vs absent	2.40 (1.24–4.72)	0.0099
Lymphatic invasion, present vs absent	3.12 (1.38–7.42)	0.0077
cT ≥ 3, yes vs no	0.76 (0.38–1.52)	0.4365
pN1 vs pN0/pNx	1.03 (0.37–2.81)	0.9477

The binary logistic model included all 187 recurrent patients: 84 with recurrence at < 12 months and 103 at ≥ 12 months (reference). Tumor size, high grade, tumor necrosis, lymphatic invasion, cT ≥ 3, and pN1 were entered simultaneously. CIs are profile-likelihood intervals; P values are two-sided Wald tests. No multiplicity adjustment was applied. The model evaluates timing conditional on observed recurrence, not recurrence risk in the full surgical cohort. aOR, adjusted odds ratio; CI, confidence interval.

In the exploratory three-group model, lymphatic invasion was associated with recurrence at < 6 versus ≥ 12 months (aOR 4.49, 95% CI 1.82–11.55; P = 0.0013), while tumor necrosis was associated with recurrence at 6 to < 12 versus ≥ 12 months (aOR 2.88, 95% CI 1.25–6.85; P = 0.0139). The corresponding estimates for lymphatic invasion at 6 to < 12 months (aOR 1.63, 95% CI 0.51–4.93; P = 0.3946) and necrosis at < 6 months (aOR 2.08, 95% CI 0.93–4.67; P = 0.0740) were also above 1 but less conclusive (Supplementary Table S2). Direct comparison of < 6 versus 6 to < 12 months did not establish a difference for either lymphatic invasion (aOR 2.76, 95% CI 0.91–8.37; P = 0.0731) or necrosis (aOR 0.72, 95% CI 0.27–1.88; P = 0.5028; Supplementary Table S3). In binary sensitivity analyses, the associations of necrosis and lymphatic invasion with first-year recurrence persisted after restriction to cM0 or adjustment for recorded M1NED status. In clear-cell RCC alone, the necrosis association remained statistically significant (aOR 2.18, 95% CI 1.04–4.59; P = 0.0400), whereas the lymphatic-invasion estimate was less precise (aOR 2.21, 95% CI 0.83–5.87; P = 0.1116; Supplementary Table S4).

Post-recurrence survival

All 187 recurrent patients were included in the PR-OS analysis, and 86 died. Median PR-OS was shorter after recurrence at < 12 months than after recurrence at ≥ 12 months: 50.6 months (95% CI 34.6–70.0) versus 82.0 months (95% CI 59.5–106.3; log-rank P = 0.0032; Table 3; Fig. 2). In the exploratory three-group comparison, median PR-OS was 49.5 months after recurrence at < 6 months, 50.6 months after recurrence at 6 to < 12 months, and 82.0 months after recurrence at ≥ 12 months (overall log-rank P = 0.0082; Fig. 3). The two first-year groups did not differ significantly (log-rank P = 0.4234); this finding does not establish equivalence.

Table 3
Post-recurrence overall survival by recurrence interval

Recurrence interval	Patients	Deaths	Censored	Median PR-OS, months (95% CI)
< 12 months	84	52	32	50.6 (34.6–70.0)
≥ 12 months	103	34	69	82.0 (59.5–106.3)
< 6 months	47	31	16	49.5 (17.9–79.9)
6 to < 12 months	37	21	16	50.6 (34.6–79.1)
≥ 12 months	103	34	69	82.0 (59.5–106.3)

The first two rows describe the main one-year comparison (log-rank P = 0.0032). The final three rows describe the exploratory three-group analysis (overall log-rank P = 0.0082). The exploratory comparison of < 6 versus 6 to < 12 months yielded P = 0.4234 and does not establish equivalence. All 187 recurrent patients were included. One patient in the ≥ 12-month group was censored on the recurrence date (time zero); no artificial positive follow-up interval was assigned. Survival was measured from recurrence. Median CIs use inversion of log–log Greenwood confidence limits. PR-OS, post-recurrence overall survival; CI, confidence interval.

In univariable Cox analyses, recurrence at < 12 months was associated with shorter PR-OS than that at ≥ 12 months (hazard ratio [HR] 1.90, 95% CI 1.23–2.93; P = 0.0038). Older age (HR per year 1.026, 95% CI 1.004–1.049; P = 0.0221) and tumor necrosis (HR 1.66, 95% CI 1.08–2.54; P = 0.0196) were also associated with shorter PR-OS. The association between lymphatic invasion and PR-OS was not statistically significant (HR 1.44, 95% CI 0.90–2.31; P = 0.1316; Table 4).

Table 4
Cox regression analyses of post-recurrence overall survival

Variable	Univariable HR (95% CI)	P	Model 1 HR (95% CI)	P	Model 2 HR (95% CI)	P
Recurrence < 12 vs ≥ 12 months	1.90 (1.23–2.93)	0.0038	1.81 (1.15–2.84)	0.0098	1.72 (1.09–2.72)	0.0203
Age at diagnosis, per year	1.026 (1.004–1.049)	0.0221	1.024 (1.002–1.047)	0.0326	1.023 (1.001–1.046)	0.0380
Tumor necrosis, present vs absent	1.66 (1.08–2.54)	0.0196	1.30 (0.83–2.03)	0.2497	1.34 (0.85–2.09)	0.2052
Lymphatic invasion, present vs absent	1.44 (0.90–2.31)	0.1316	—	—	1.31 (0.80–2.12)	0.2838

All models included 187 patients and 86 deaths. One patient was censored on the recurrence date and contributed no subsequent time at risk. Univariable estimates are from separate models. Model 1 (primary): recurrence timing, age at diagnosis, and tumor necrosis. Model 2: Model 1 plus lymphatic invasion. All covariates in each adjusted model were entered simultaneously. A dash denotes a variable not included in that model. Ties were handled using the Breslow method; CIs and P values are two-sided Wald estimates. Additional sensitivity analyses and proportional-hazards diagnostics are provided in Online Resource 1. HR, hazard ratio; CI, confidence interval.

After adjustment for age and tumor necrosis, recurrence at < 12 months remained associated with shorter PR-OS than recurrence at ≥ 12 months (HR 1.81, 95% CI 1.15–2.84; P = 0.0098). The association remained statistically significant after adding lymphatic invasion to this model (HR 1.72, 95% CI 1.09–2.72; P = 0.0203). Lymphatic invasion itself was not significantly associated with PR-OS in this adjusted model (HR 1.31, 95% CI 0.80–2.12; P = 0.2838; Table 4). Survival sensitivity analyses are reported in Online Resource 1 (Supplementary Table S5), with additional exploratory three-group sensitivity analyses in Supplementary Table S6. Proportional-hazards diagnostics are shown in Supplementary Fig. S1.

Discussion

In this multicenter cohort, tumor necrosis and lymphatic invasion were associated with recurrence within 1 year among patients who recurred, after adjustment for tumor size, grade, clinical T category, and pathological nodal status. Recurrence within 1 year was also associated with poorer PR-OS. The main pathological model included all six covariates, with six slope coefficients compared with 12 in the exploratory three-group model.

These survival findings are consistent with those of previous reports linking shorter recurrence intervals to adverse outcomes [8–11]. Eggener et al. incorporated an interval shorter than 12 months into prognostic assessment post-recurrence [8]. In our cohort, the association persisted after additional

adjustment for lymphatic invasion. These findings support the prognostic relevance of the 1-year comparison but do not demonstrate improved prediction beyond established models or a benefit from changing clinical management. Similar estimates in cM0-restricted and M1NED-adjusted analyses suggest that the principal findings were not solely attributable to the inclusion of M1NED.

The association of lymphatic invasion with first-year recurrence may reflect earlier clinical manifestation of disseminated disease. Previous studies support the prognostic relevance of lymphovascular or microvascular invasion [5, 10, 15], although these categories differ from lymphatic invasion alone. Our data did not directly measure occult metastases or establish a dissemination mechanism. In clear-cell RCC alone, the lymphatic-invasion estimate remained in the same direction but its CI included 1, limiting histology-specific conclusions.

Necrosis is an established adverse prognostic feature [3, 16], and its association with recurrence during the first year is consistent with previous findings [12]. Both necrosis and lymphatic invasion were associated with first-year recurrence in the main binary model. The three-group analysis adds descriptive detail: the lymphatic-invasion point estimate was larger for recurrence at < 6 months, whereas the necrosis point estimate was larger for recurrence at 6 to < 12 months, each relative to ≥ 12 months. This pattern raises the hypothesis that pathological correlates of recurrence timing may vary within the first postoperative year and provides a rationale for examining these intervals in larger cohorts. However, the direct first-year contrasts were inconclusive. Statistical significance in one comparison with ≥ 12-month recurrence but not another does not establish a difference between the two earlier intervals. Given the small subgroups, 12 slope coefficients, and multiple comparisons without adjustment, this pattern is hypothesis-generating and may reflect sampling variability. These findings neither establish distinct biological types of early recurrence nor validate 6 months as an optimal cutoff; the two-group analysis remains the principal pathological result.

Recurrence timing may help contextualize prognosis once recurrence has occurred. The pathological associations warrant further investigation but do not establish indications for intensified imaging or adjuvant pembrolizumab. Our cohort included non-clear-cell cancers and did not reproduce all KEYNOTE-564 eligibility criteria [6, 7]. Thus, surveillance should continue to follow established risk assessments and relevant evidence [1, 17, 18], consistent with current European Association of Urology guidance [19].

This study has some limitations, including retrospective selection, incomplete patient-level documentation of the original screening decisions, heterogeneous grading and surveillance, and exploratory model development without external validation. The main binary model included six slope coefficients, whereas the exploratory three-group model included 12; both were subject to unstable estimates and overfitting. Analyses conditioned on observed recurrence do not estimate recurrence risk in all surgical patients and may be affected by selection related to follow-up duration. M1NED classification was supported by investigator clarification; however, exact complete-resection and NED dates were unavailable. Using renal surgery as the common origin may misclassify recurrence intervals if NED was attained later; the inclusion of patients rendered NED after surgery may also introduce timing-

related selection bias. The small M1NED subgroup precludes subgroup-specific conclusions. Survival adjustment was limited: recurrence burden was incompletely documented; age at diagnosis, rather than at recurrence, was used; and performance status, comorbidity, and subsequent treatment were not modeled. Center effects could not be assessed because center identifiers were unavailable. Sensitivity estimates were less precise. Cox hazard ratios summarize associations across follow-up and may not be constant over time (Online Resource 1, Supplementary Fig. S1).

In conclusion, tumor necrosis and lymphatic invasion were associated with recurrence within 1 year among patients who recurred. First-year recurrence was associated with worse survival after recurrence in this cohort, which included patients registered as M1NED. External validation is needed before these findings can inform surveillance or treatment.

Declarations

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Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee for Life Science and Medical Research of Hokkaido University Hospital (approval no. Sei024-0095). Permission to conduct the study at Hokkaido University Hospital was granted by the hospital director on 13 September 2024 (institutional study no. Shi024-0218). The protocol required compliance with the Declaration of Helsinki and the Japanese Ethical Guidelines for Life Science and Medical Research Involving Human Subjects, together with institutional permission at participating centers. Individual written informed consent was not required under the protocol, which specified public disclosure of study information and an opportunity for patients or their representatives to decline participation.

Author contributions

Tsuyoshi Matsuda and Kojiro Ohba contributed to the study conception and design. Tsuyoshi Matsuda, Masaharu Oki, Ken Kawada, Tomokazu Sazuka, Keisuke Ando, Kazuyuki Numakura, Yuya Sekine, Keita Minami, Toru Harabayashi, Sei Naito, Norihiko Tsuchiya, Yu Kujiraoka, and Haruka Miyata collected clinical data. Tsuyoshi Matsuda performed the literature search. Tsuyoshi Matsuda and Kojiro Ohba

performed the statistical analyses and drafted the manuscript. Kojiro Ohba revised the manuscript. Ryoichi Imamura supervised the study.

Data availability

Individual-level data are not publicly available because of patient confidentiality and institutional restrictions. Data-access requests may be addressed to the corresponding author for review by the coordinating institution and participating centers. Secondary use requires appropriate ethical and institutional authorization.

AI-assisted work

ChatGPT was used to assist with drafting, translation, language revision, code preparation, statistical computation, and data-audit support. Statistical estimates were generated programmatically from the study data, and figures were created using Matplotlib; generative image tools were not used to create scientific figures.

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Figures

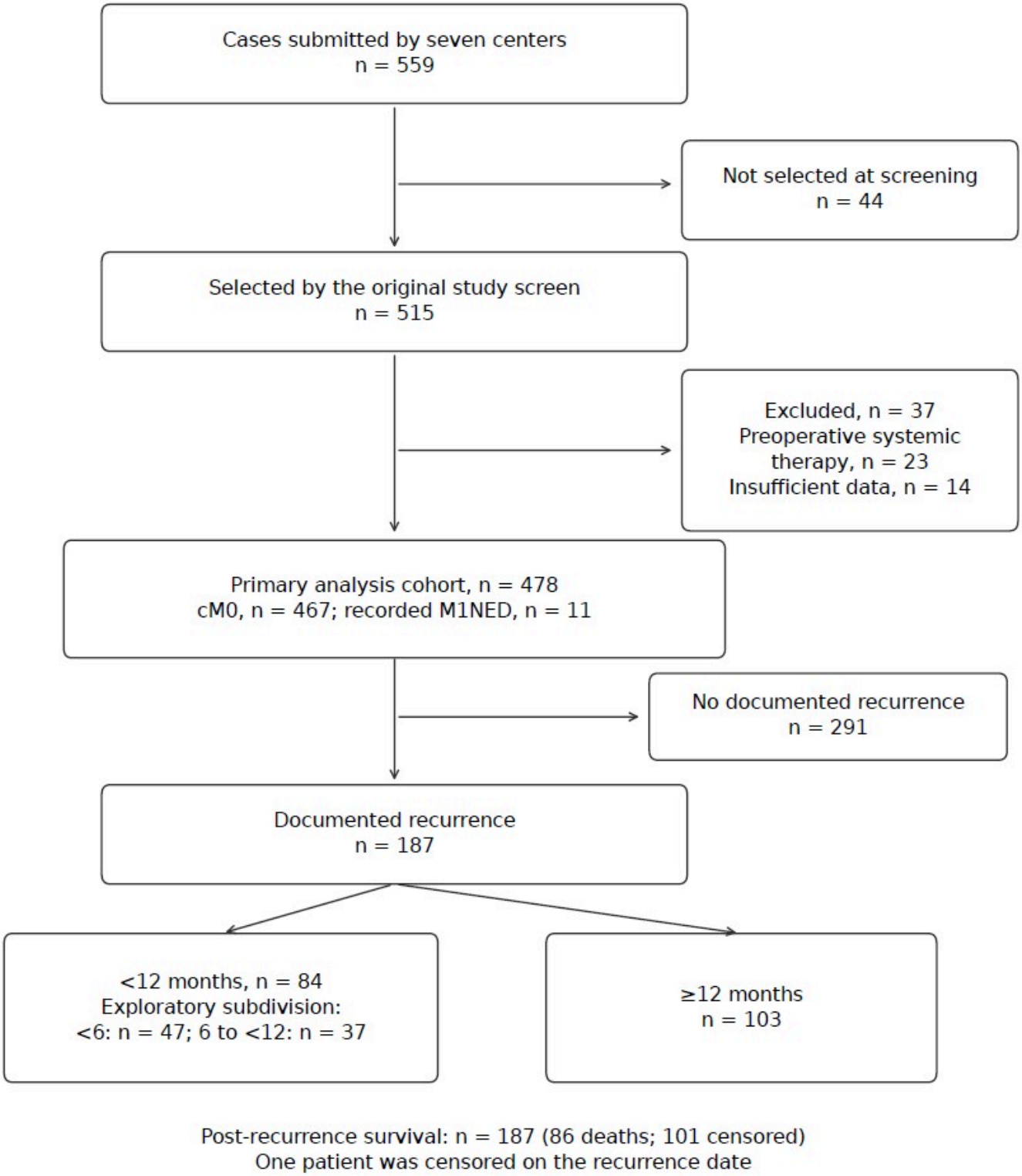
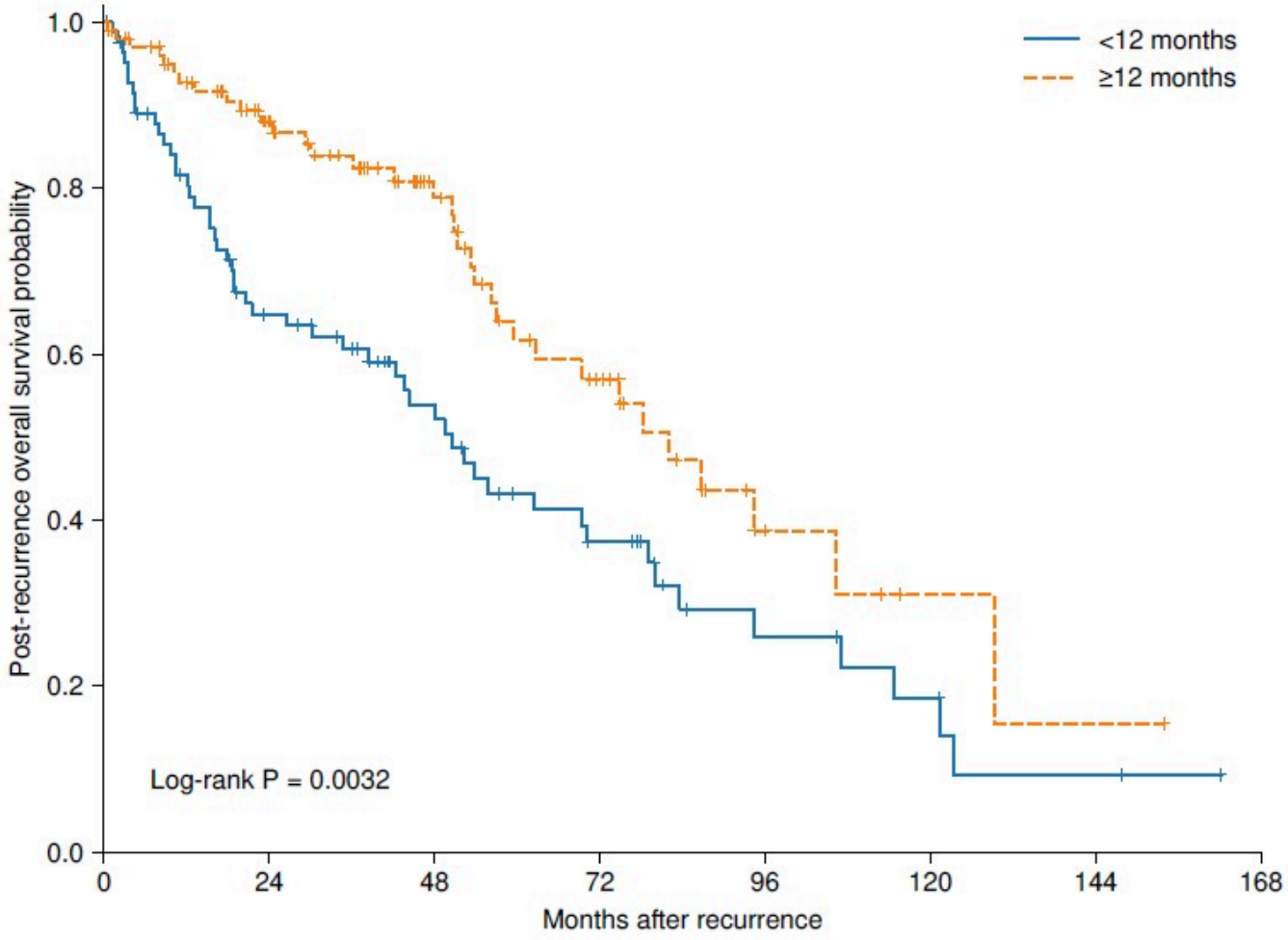


Figure 1

Patient selection and analysis populations. Of 559 submitted cases, 515 passed the original investigator screen; 23 patients who received preoperative systemic therapy and 14 with insufficient data were excluded. The primary cohort comprised 478 patients, including 467 cM0 patients and 11 cM1 patients

registered as M1NED. All 187 patients with recurrence were included in the post-recurrence overall survival analysis; one was censored on the recurrence date. Recurrence groups used recorded dates and calendar-month anniversaries. NED, no evidence of disease

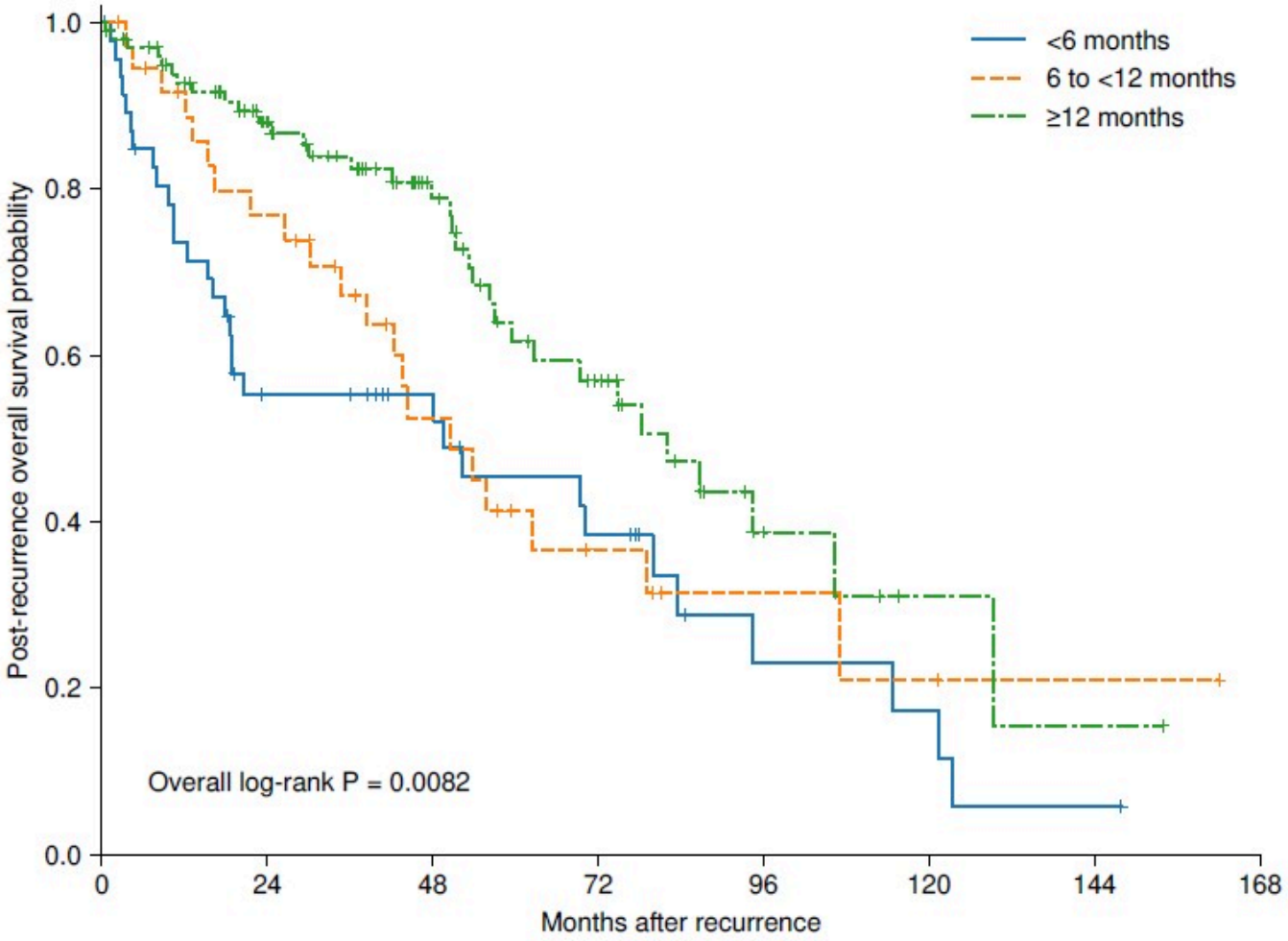


Number at risk

<12 months	84	48	31	18	8	5	2	0
≥12 months	103	67	40	22	7	2	1	0

Figure 2

Post-recurrence overall survival for recurrence at <12 versus ≥12 months. Groups included 84 and 103 patients, respectively. Step curves indicate Kaplan–Meier estimates, and plus signs indicate censoring. Numbers at risk are shown below the plot. The log-rank P value was 0.0032



Number at risk

<6 months	47	22	17	11	4	3	1	0
6 to <12 months	37	26	14	7	4	2	1	0
≥12 months	103	67	40	22	7	2	1	0

Figure 3

Post-recurrence overall survival in 187 patients by recurrence interval in an exploratory three-group comparison. Groups included 47 patients with recurrence at <6 months, 37 at 6 to <12 months, and 103 at ≥12 months. Step curves indicate Kaplan–Meier estimates, plus signs indicate censoring, and the table shows numbers at risk immediately before each stated time. The overall log-rank P value was 0.0082. The exploratory comparison of <6 versus 6 to <12 months yielded P=0.4234

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- OnlineResource1.pdf