EJMI

DOI: 10.14744/ejmi.2612571
EJMI 2026;10(4):571–582

Research Article

Predictors of Recurrence Following Curative-Intent Local Therapy for Oligometastatic Renal Cell Carcinoma: A Multicenter Retrospective Cohort Study from the Turkish Oncology Group (TOG)

Engin Hendem,[1] Gülhan Dinç,[2] Çağlayan Geredeli,[2] Nilüfer Avcı,[3] Mustafa Seyyar,[4] Umut Kefeli,[5] Nadiye Sever,[6] Osman Köstek,[6] Tugay Avcı,[7] Atike Pınar Erdoğan,[7] İlhan Hacıbekiroğlu,[8] Murat Araz,[9]

[1]Department of Medical Oncology, Erzincan Mengücek Gazi Training and Research Hospital, Erzincan, Türkiye
[2]Department of Medical Oncology, Prof. Dr. Cemil Taşcıoğlu City Hospital, İstanbul, Türkiye
[3]Department of Medical Oncology, Medicana Bursa Hospital, Bursa, Türkiye
[4]Department of Medical Oncology, Gaziantep City Hospital, Gaziantep, Türkiye
[5]Department of Medical Oncology, Kocaeli University Faculty of Medicine, Kocaeli, Türkiye
[6]Department of Medical Oncology, Marmara University Faculty of Medicine, İstanbul, Türkiye
[7]Department of Medical Oncology, Manisa Celal Bayar University Faculty of Medicine, Manisa, Türkiye
[8]Department of Medical Oncology, Sakarya University Faculty of Medicine, Sakarya, Türkiye
[9]Department of Medical Oncology, Necmettin Erbakan University Meram Faculty of Medicine, Konya, Türkiye

Abstract

Objectives: To identify clinicopathological predictors of recurrence following curative-intent local therapy in patients with oligometastatic renal cell carcinoma (RCC).

Methods: In this multicenter retrospective study, 81 oligometastatic RCC patients treated at seven Turkish centers between April 2010 and October 2022 were analyzed. All patients underwent primary tumor surgery followed by curative-intent local therapy (metastasectomy, stereotactic body radiotherapy, and/or radiofrequency ablation). Oligometastatic disease was defined as a limited metastatic burden considered amenable to complete local treatment. Recurrence-free survival (RFS) and overall survival (OS) were estimated using the Kaplan–Meier method. Cox regression analyses were performed to identify independent predictors of recurrence.

Results: Median age was 58 years, and 75.3% of patients were male. After a median follow-up of 35.1 months, median RFS was 31.4 months and median OS was 63.8 months. On pT-stratified multivariable analysis, sarcomatoid differentiation (HR=4.30, p=0.003), age (HR=1.04 per year, p=0.015), and number of metastatic organ sites (HR=1.31, p=0.028) remained independently associated with recurrence.

Conclusion: Sarcomatoid differentiation, advancing age, and greater metastatic organ burden independently predict recurrence after curative-intent local therapy in oligometastatic RCC. These factors may help inform surveillance and adjuvant treatment discussions, although external validation is required before clinical application.

Keywords: Metastasectomy, oligometastatic disease, recurrence-free survival, renal cell carcinoma, risk stratification, sarcomatoid differentiation

Cite This Article: *Hendem E, Dinç G, Geredeli Ç, Avcı N, Seyyar M, Kefeli U, et al. Predictors of Recurrence Following Curative-Intent Local Therapy for Oligometastatic Renal Cell Carcinoma: A Multicenter Retrospective Cohort Study from the Turkish Oncology Group (TOG). EJMI 2026;10(4):571–582.*

Address for correspondence: Engin HENDEM, MD. Department of Medical Oncology, Erzincan Mengücek Gazi Training and Research Hospital, Erzincan, Türkiye
Phone: +90 507 648 70 59 **E-mail:** enginhende61@gmail.com

Submitted Date: June 26, 2026 **Revised Date:** August 25, 2026 **Accepted Date:** September 14, 2026

©Copyright 2026 by Eurasian Journal of Medical Investigation - Available online at www.ejmi.org
OPEN ACCESS This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Renal cell carcinoma (RCC) accounts for approximately 2–3% of all adult malignancies, with clear cell histology constituting the predominant subtype.[1,2] Although most patients present with localized disease amenable to curative-intent surgery, approximately 20–30% develop metachronous distant metastases during follow-up, and up to 30% present with synchronous metastatic disease at diagnosis.[3,4]

The oligometastatic state—originally conceptualized by Hellman and Weichselbaum[5]—describes a limited burden of metastatic disease occupying an intermediate position between truly localized disease and widespread systemic dissemination. While earlier definitions often referenced a threshold of three to five lesions, evolving clinical practice recognizes that the concept is better captured by the feasibility of complete local treatment rather than a strict numerical cutoff.[6,7] RCC, with its immunogenic tumor biology and propensity for late, isolated metastases, is one of the malignancies in which the oligometastatic concept holds particular clinical relevance.[8]

Curative-intent local therapies for oligometastatic RCC—including surgical metastasectomy, SBRT, and RFA—have demonstrated favorable long-term outcomes in appropriately selected patients.[9–11] Alt et al.[9] reported 5-year cancer-specific survival rates of up to 49.4% following complete metastasectomy in selected RCC patients, and Hofmann et al.[12] demonstrated favorable outcomes after pulmonary resection of RCC metastases. SBRT has shown promising local control rates exceeding 90% in oligometastatic RCC.[13] Despite these encouraging results, recurrence following curative-intent therapy remains common. Identifying patients at highest risk is critical for optimizing surveillance and for selecting candidates who might benefit from additional systemic therapy.

The adjuvant therapy field for RCC has evolved following the KEYNOTE-564 trial, which demonstrated a significant disease-free survival benefit with adjuvant pembrolizumab in high-risk localized and locally advanced RCC, including a subgroup of patients rendered disease-free after metastasectomy (HR=0.68; 95% CI 0.53–0.87; p<0.001).[14] The identification of prognostic factors in the oligometastatic setting may have relevance for informing discussions about adjuvant treatment, though the present study was designed to identify prognostic factors for recurrence rather than to evaluate treatment efficacy.

Despite the growing body of evidence supporting local therapy in oligometastatic RCC, the prognostic factors that predict recurrence in this specific population remain incompletely characterized. Most published prognostic models, including the International Metastatic RCC Database Consortium (IMDC) model[15], were developed and validated in systemic therapy–treated populations with widespread metastatic disease and may not be directly applicable to the oligometastatic setting.

The purpose of this multicenter study was to identify clinicopathological risk factors associated with recurrence following curative-intent local therapy in oligometastatic RCC patients, with the aim of generating hypotheses for risk stratification that can inform future prospective studies and contribute to evolving discussions around surveillance planning.

Materials and Methods

Study Design and Population

This multicenter, retrospective cohort study included oligometastatic RCC patients treated at seven academic and tertiary referral centers in Türkiye between April 2010 and October 2022, with follow-up through December 2023. This study was conducted under the auspices of the Turkish Oncology Group (TOG).

Ethics Approval

Ethical approval for this multicenter retrospective study was obtained from the Necmettin Erbakan University Non-Pharmaceutical and Medical Device Research Ethics Committee (no: 2022/4013, date: 21.10.2022). The study was conducted in accordance with the Declaration of Helsinki. Due to the retrospective nature of the study, informed consent requirements were handled according to institutional regulations.

Eligibility Criteria

Patients were eligible for inclusion if they met the following criteria: (i) histologically confirmed RCC; (ii) surgical management of the primary renal tumor (radical or partial nephrectomy); (iii) limited metastatic burden considered amenable to complete local treatment, encompassing both synchronous and metachronous presentations; (iv) receipt of curative-intent local therapy directed at metastatic sites (metastasectomy, SBRT, or RFA); and (v) availability of adequate follow-up data. Patients with diffuse, widely disseminated metastatic disease not amenable to curative-intent local treatment were excluded.

Patients were selected by multidisciplinary tumor boards at each participating center based on the feasibility of achieving complete local treatment of all visible metastatic deposits, irrespective of a strict lesion-count threshold. This pragmatic selection reflects real-world practice but extends beyond classical oligometastatic definitions (typically ≤3–5 lesions), which should be considered when interpreting

our findings. Consequently, the cohort includes patients with a range of metastatic burden (up to 6 organ sites involved and up to 22 total lesions), provided that the multidisciplinary team at each center deemed all sites amenable to definitive local therapy. This broader inclusion mirrors real-world patterns and enhances generalizability, though it also introduces heterogeneity that should be considered when interpreting results and limits comparability with studies that used stricter oligometastatic definitions.

Data Collection

Clinical data were retrospectively collected from institutional databases and included patient demographics (age at diagnosis, sex, ECOG performance status); primary tumor characteristics (laterality, surgical approach, tumor size, pathological T stage [pT], Fuhrman nuclear grade, sarcomatoid differentiation, tumor necrosis, lymphovascular invasion [LVI]); metastasis characteristics (synchronous versus metachronous, sites of involvement, number of metastatic organ sites, disease-free interval [DFI]); type of curative-intent local therapy; laboratory parameters at metastasis detection (hemoglobin, serum calcium, neutrophil count, lactate dehydrogenase [LDH], platelet count); and survival outcomes.

Missing data were present for several pathological variables due to the retrospective, multicenter nature of the study. The extent of missingness ranged from 0% (age, sex) to approximately 11% (Fuhrman grade, with 9 of 81 cases lacking data). Other variables with notable missingness included tumor necrosis (8 missing, 9.9%), sarcomatoid differentiation (6 missing, 7.4%), LVI (6 missing, 7.4%), and surgical approach (8 missing, 9.9%). Curative treatment dates were unavailable for 17 patients (21.0%), who were consequently excluded from time-to-event analyses. One additional patient was excluded from OS analysis due to a data entry error yielding a negative survival time. Analyses for each variable were conducted on the subset of patients with available data, and the number of evaluable cases is reported alongside each result. Multiple imputation was not performed given the relatively low overall rates of missingness for pathological variables and the exploratory nature of the risk-stratification model.

Outcomes and Definitions

The primary endpoint was RFS, defined as the interval from curative-intent local therapy for metastatic disease to the first documented recurrence, disease progression, or last follow-up (censored). The secondary endpoint was OS, defined as the interval from curative-intent local therapy to death from any cause or last follow-up (censored). Synchronous metastases were defined as metastatic disease identified at or within one month of the primary RCC diagnosis. The disease-free interval (DFI) was calculated from primary tumor surgery to the first documented metastasis.

Statistical Analysis

Descriptive statistics were presented as median with interquartile range (IQR) or range for continuous variables and as frequencies with percentages for categorical variables. Survival estimates were calculated using the Kaplan–Meier method, and intergroup comparisons were performed using the log-rank test.

Univariate Cox proportional hazards regression analysis was performed to evaluate the association between clinicopathological variables and RFS. Variables with $p<0.10$ on univariate analysis, along with clinically relevant covariates, were considered for inclusion in the multivariate model. The proportional hazards (PH) assumption was assessed for each covariate using Schoenfeld residuals. Pathological T stage violated the PH assumption (Schoenfeld test, $p=0.037$) and was therefore incorporated as a stratification variable rather than a covariate in the multivariate model.

The multivariate model was constructed with attention to the events-per-variable (EPV) criterion, targeting a minimum EPV ≥ 10 to ensure model stability[16] Given 37 recurrence events in the RFS analysis cohort, a maximum of three covariates were included (37 events ÷ 3 covariates ≈ 12.3 EPV). Results were expressed as hazard ratios (HR) with 95% confidence intervals (CI). All tests were two-sided, and $p<0.05$ was considered statistically significant.

Statistical analyses were performed using Python version 3.11 (Python Software Foundation, Wilmington, DE, USA). Survival analyses were conducted using the lifelines (version 0.27), SciPy, and statsmodels libraries.

Results

Patient Demographics and Clinical Characteristics

A total of 81 oligometastatic RCC patients from seven centers were included. The median age was 58 years (range 29–83; IQR 49–64), and 61 patients (75.3%) were male. ECOG performance status was 0 in 34 patients (42.0%), 1 in 36 patients (44.4%), and ≥2 in 11 patients (13.6%). The median primary tumor size was 7.5 cm (IQR 5.5–9.0). The majority of patients underwent radical nephrectomy (n=58; 79.5% of 73 evaluable), with 15 patients (20.5%) undergoing partial nephrectomy; surgical approach data were unavailable for 8 patients. On histopathological examination, Fuhrman grade 3–4 disease was present in 48 of 72 evaluable patients (66.7%), pT3–4 stage in 23 of 77 evaluable patients (29.9%), sarcomatoid differentiation in 15 of 75 evaluable patients (20.0%), tumor necrosis in 41 of

73 evaluable patients (56.2%), and LVI in 33 of 75 evaluable patients (44.0%).

In the full cohort of 81 patients, 28 patients (34.6%) had died and 53 (65.4%) were alive at last follow-up. One patient had an indeterminate vital status record and was classified based on last contact data.

The distribution of metastatic sites is shown in Supplementary Figure S1. Patient demographics and clinical characteristics are summarized in Table 1.

Metastasis Characteristics and Treatment

Synchronous metastases were present in 35 patients (43.2%), while 46 patients (56.8%) developed metachronous metastatic disease with a median DFI of 11.0 months (IQR 0.0–42.4). The most common sites of metastasis were lung (n=44; 54.3%), bone (n=35; 43.8%), mediastinal lymph nodes (n=20; 24.7%), abdominal lymph nodes (n=15; 18.5%), brain (n=12; 14.8%), and liver (n=7; 8.6%) (Fig. S1). The median number of metastatic organ sites was 2 (range 1–6 among 78 evaluable patients), reflecting the clinically

Table 1. Patient demographics and clinical characteristics (N=81)

Variable	Category	n (%) or Median (Range)	N evaluable
Age (years)	—	58 (29–83); IQR 49–64	81
Sex	Male	61 (75.3%)	81
	Female	20 (24.7%)	
ECOG PS	0	34 (42.0%)	81
	1	36 (44.4%)	
	≥2	11 (13.6%)	
Tumor size (cm)	—	7.5 (IQR 5.5–9.0)	81
Surgery type	Radical nephrectomy	58 (79.5%)	73
	Partial nephrectomy	15 (20.5%)	
Fuhrman grade	1–2	24 (33.3%)	72
	3–4	48 (66.7%)	
pT stage	T1–T2	54 (70.1%)	77
	T3–T4	23 (29.9%)	
Sarcomatoid differentiation	Present	15 (20.0%)	75
Tumor necrosis	Present	41 (56.2%)	73
LVI	Present	33 (44.0%)	75
Metastasis timing	Synchronous	35 (43.2%)	81
	Metachronous	46 (56.8%)	
Metastatic sites	Lung	44 (54.3%)	81
	Bone	35 (43.8%)	80
	Mediastinal LN	20 (24.7%)	81
	Abdominal LN	15 (18.5%)	81
	Brain	12 (14.8%)	81
	Liver	7 (8.6%)	81
Metastatic organ sites	—	2 (1–6)†	81
DFI (months)	—	11.0 (IQR 0.0–42.4)	81
Vital status	Alive	53 (65.4%)	81
	Deceased	28 (34.6%)	

DFI: Disease-free interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IQR: Interquartile range; LN: Lymph node; LVI: Lymphovascular invasion. Percentages for surgery type, Fuhrman grade, pT stage, sarcomatoid differentiation, tumor necrosis, and LVI are calculated from the number of evaluable cases. All other percentages are calculated from N=81. †Metastatic organ-site distribution reported among 78 evaluable patients; three patients lacked site-level documentation. Missing data: Surgery type (8 patients, 9.9%), Fuhrman grade (9, 11.1%), pT stage (4, 4.9%), sarcomatoid differentiation (6, 7.4%), tumor necrosis (8, 9.9%), LVI (6, 7.4%), bone metastasis (1, 1.2%).

heterogeneous nature of disease considered amenable to complete local treatment. Three patients had no metastatic organ sites recorded in the database despite meeting inclusion criteria for curative-intent local therapy; these cases likely reflect incomplete site-level documentation rather than absence of metastatic disease and were retained in the analysis.

Curative-intent local therapy for metastatic disease included surgical metastasectomy (n=48; 59.3%) and SBRT (n=34; 42.0%), with RFA used in 1 patient (1.2%). Treatment categories were not mutually exclusive: 11 patients (13.6%) received combined surgical resection and SBRT for different metastatic sites. The choice of modality was determined by the treating team at each center based on anatomical location, number of lesions, and patient fitness.

Survival Outcomes

Of the 81 enrolled patients, 64 had documented curative treatment dates and valid survival time calculations for RFS analysis and 63 for OS analysis. The remaining patients lacked curative treatment dates (n=17) or had data entry errors precluding valid survival time computation (n=1); these patients were excluded from Kaplan–Meier and Cox regression analyses but are included in descriptive statistics.

After a median follow-up of 35.1 months among surviving patients, 28 patients (34.6%) in the full cohort had died. Within the RFS analysis cohort (n=64), 37 recurrence events were identified. Median RFS was 31.4 months. The 12-month, 24-month, and 36-month RFS rates were 68.4%, 52.5%, and 37.9%, respectively.

Within the OS analysis cohort (n=63), 21 deaths were observed. Median OS was 63.8 months, and the 12-month, 24-month, and 36-month OS rates were 91.2%, 81.1%, and 71.2%, respectively. These OS estimates should be interpreted cautiously given the limited number of death events (n=21), which yields wide confidence intervals and limited statistical precision. RFS, with 37 events in 64 patients, represents the more statistically mature and primary endpoint in this analysis. Survival probabilities at key time points are shown in Supplementary Figure S2. Kaplan–Meier survival estimates for RFS and OS are shown in Figure 1.

Univariate Analysis of Risk Factors for Recurrence

Univariate Cox regression analysis identified four statistically significant predictors of RFS: sarcomatoid differentiation (HR=3.19; 95% CI 1.55–6.58; p=0.002), age (per year; HR=1.03; 95% CI 1.00–1.07; p=0.038), number of metastatic organ sites (HR=1.36; 95% CI 1.05–1.75; p=0.018), and bone metastasis (HR=1.99; 95% CI 1.05–3.77; p=0.035). High pT stage (T3–4) was not significantly associated with RFS in univariate Cox analysis (HR=1.71; 95% CI 0.86–3.42; p=0.127). Sex, ECOG performance status, synchronous versus metachronous presentation, tumor size, Fuhrman grade, necrosis, LVI, lung metastasis, and IMDC-associated laboratory parameters (hemoglobin, LDH, platelets) were not significantly associated with RFS in this cohort. Kaplan–Meier analyses stratified by individual variables are presented in Supplementary Figures S3–S6. The results of univariate Cox regression analysis are presented in Table 2 and Figure 2.

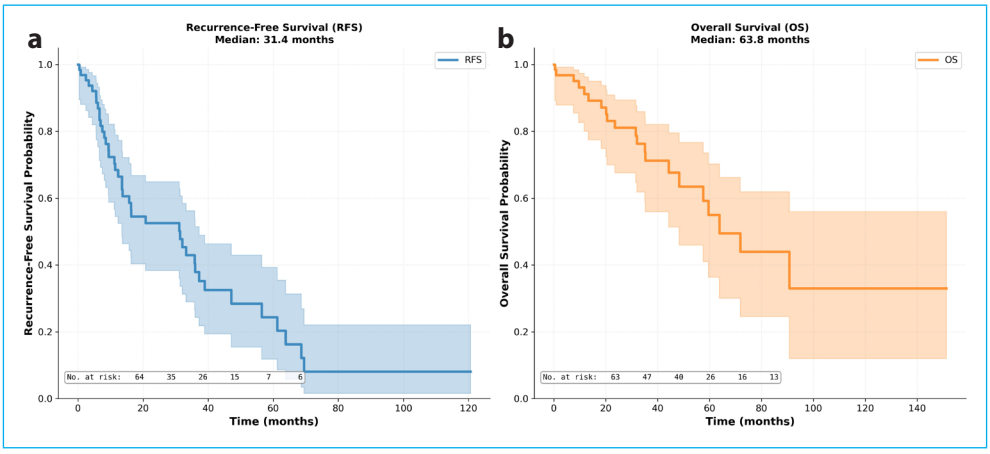


Figure 1. Kaplan–Meier survival estimates for the study cohort. **(a)** Recurrence-free survival (RFS) in 64 evaluable patients. Median RFS was 31.4 months (37 events). The 12-month and 36-month RFS rates were 68.4% and 37.9%, respectively. **(b)** Overall survival (OS) in 63 evaluable patients. Median OS was 63.8 months (21 events). The 12-month and 36-month OS rates were 91.2% and 71.2%, respectively. Shaded areas represent 95% confidence intervals. Numbers at risk are shown below the x-axis. OS estimates are based on only 21 death events and should be interpreted with appropriate caution.

Table 2. Univariate Cox regression analysis for recurrence-free survival

Variable	HR	95% CI	p	n
Age (per year)	1.03	1.00–1.07	0.038	62
Sarcomatoid differentiation	3.19	1.55–6.58	0.002	61
High grade (3–4 vs 1–2)	1.30	0.67–2.51	0.440	60
High pT stage (T3–4 vs T1–2)	1.71	0.86–3.42	0.127	62
Lymphovascular invasion	1.04	0.55–1.98	0.901	61
Tumor necrosis	1.04	0.55–1.98	0.903	59
Tumor size (per cm)	1.04	0.96–1.13	0.351	62
Number of metastatic organ sites	1.36	1.05–1.75	0.018	62
Synchronous metastasis	1.16	0.59–2.30	0.668	62
Bone metastasis	1.99	1.05–3.77	0.035	61
Lung metastasis	0.83	0.44–1.58	0.569	62
Brain metastasis	2.36	0.81–6.87	0.116	62
ECOG PS	1.04	0.63–1.72	0.877	62
Low hemoglobin	1.12	0.60–2.11	0.726	62
Elevated LDH	0.84	0.44–1.60	0.590	61
Thrombocytosis	1.65	0.63–4.26	0.305	61

Statistically significant variables (p<0.05) are shown in bold. CI: Confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: Hazard ratio; LDH: Lactate dehydrogenase.

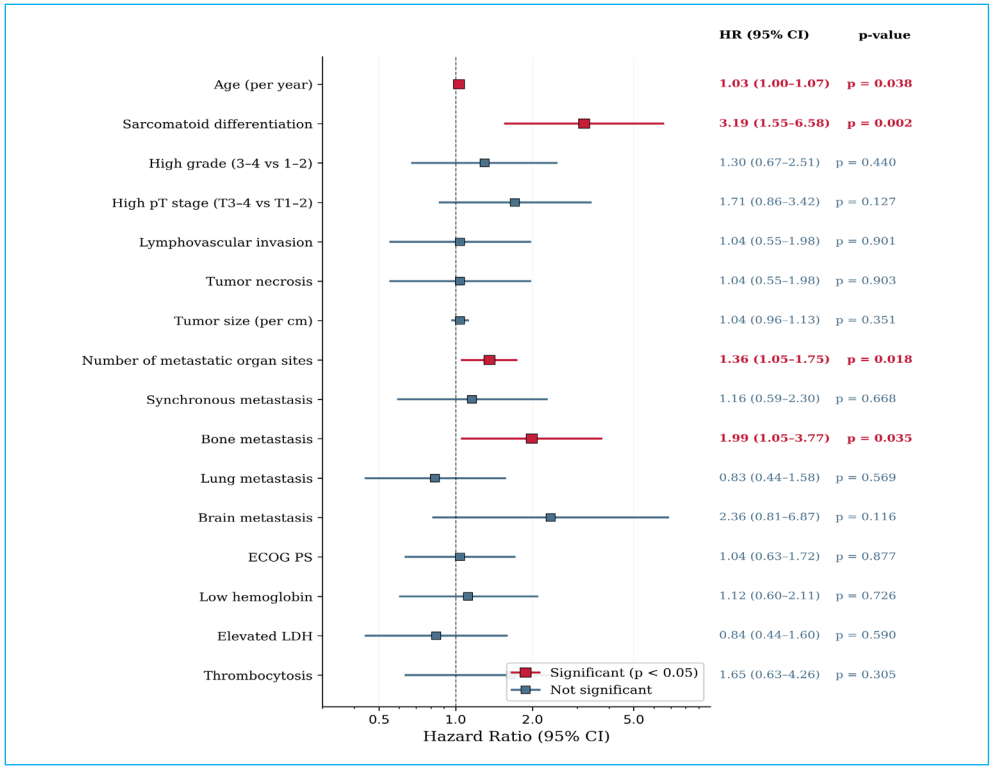


Figure 2. Forest plot of univariate Cox regression analysis for RFS. Hazard ratios with 95% confidence intervals are shown on a logarithmic scale. Red markers indicate statistically significant variables (p<0.05): sarcomatoid differentiation (HR=3.19; p=0.002), bone metastasis (HR=1.99; p=0.035), number of metastatic organ sites (HR=1.36; p=0.018), and age (HR=1.03 per year; p=0.038). The dashed vertical line represents HR=1.0 (no effect).

Table 3. Multivariate Cox regression analysis (stratified by pT stage)

Variable	HR	95% CI	p
Sarcomatoid differentiation	4.30	1.65–11.17	0.003
Age (per year)	1.04	1.01–1.07	0.015
Number of metastatic organ sites	1.31	1.03–1.68	0.028

Model stratified on pathological T stage (pT1–2 vs. pT3–4) due to violation of the proportional hazards assumption (Schoenfeld test, p=0.037). Events per variable: 37 events ÷ 3 covariates=12.3. CI: Confidence interval; HR: Hazard ratio

Multivariate Analysis

Assessment of the PH assumption revealed that pT stage violated proportionality (Schoenfeld test, p=0.037), indicating a time-varying effect. Accordingly, pT stage was incorporated as a stratification variable. A parsimonious three-predictor model was fitted, adhering to the EPV ≥ 10 criterion (37 events ÷ 3 predictors=12.3 EPV). The pT-stratified multivariate Cox model identified three independent predictors of recurrence:

- Sarcomatoid differentiation: HR=4.30 (95% CI 1.65–11.17; p=0.003)
- Age (per year): HR=1.04 (95% CI 1.01–1.07; p=0.015)
- Number of metastatic organ sites: HR=1.31 (95% CI 1.03–1.68; p=0.028)

The results of the pT-stratified multivariate Cox regression analysis are shown in Table 3 and Figure 3.

Exploratory Risk Stratification

An exploratory composite risk score was derived from the three independent prognostic factors: sarcomatoid differentiation (+2 points, reflecting its comparatively stronger prognostic effect in the multivariable model), age ≥60 years (+1 point; selected as a pragmatic, clinically interpretable threshold close to the cohort median age of 58 years, while age was retained as a continuous variable in the primary Cox analyses), and >2 metastatic organ sites (+1 point). Patients in the RFS analysis cohort were categorized into low-risk (score=0; n=23), intermediate-risk (score=1; n=22), and high-risk (score ≥2; n=19) groups. Kaplan–Meier analysis demonstrated divergent RFS curves across the three risk groups (overall log-rank p<0.001). In the high-risk group, 17 of 19 patients (89.5%) experienced recurrence, compared with 14 of 22 (63.6%) in the intermediate-risk group and 6 of 23 (26.1%) in the low-risk group.

This risk score was derived and evaluated within the same dataset and has not undergone external validation. Its apparent discriminatory ability may be inflated by overfitting. The score should be regarded as hypothesis-generating rather than as a validated clinical tool. Prospective external validation is required before any consideration for clinical

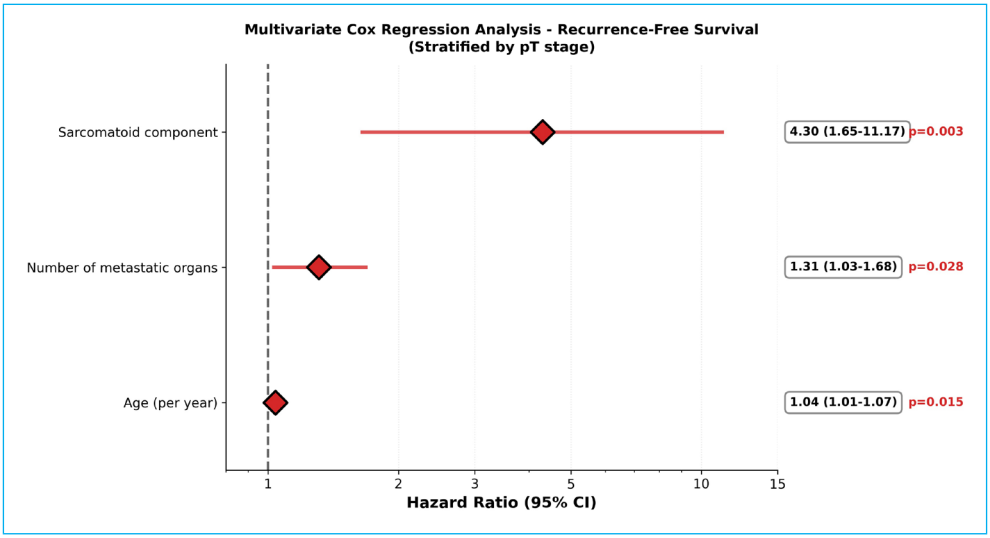


Figure 3. Forest plot of multivariate Cox regression analysis for RFS (stratified on pT stage). Three independent predictors of recurrence are displayed with hazard ratios and 95% confidence intervals on a logarithmic scale. Sarcomatoid differentiation was the strongest predictor (HR=4.30; p=0.003), followed by age (HR=1.04 per year; p=0.015) and number of metastatic organ sites (HR=1.31; p=0.028). All p<0.05. Supplementary Figure S5 shows Kaplan–Meier RFS curves stratified by pT stage.

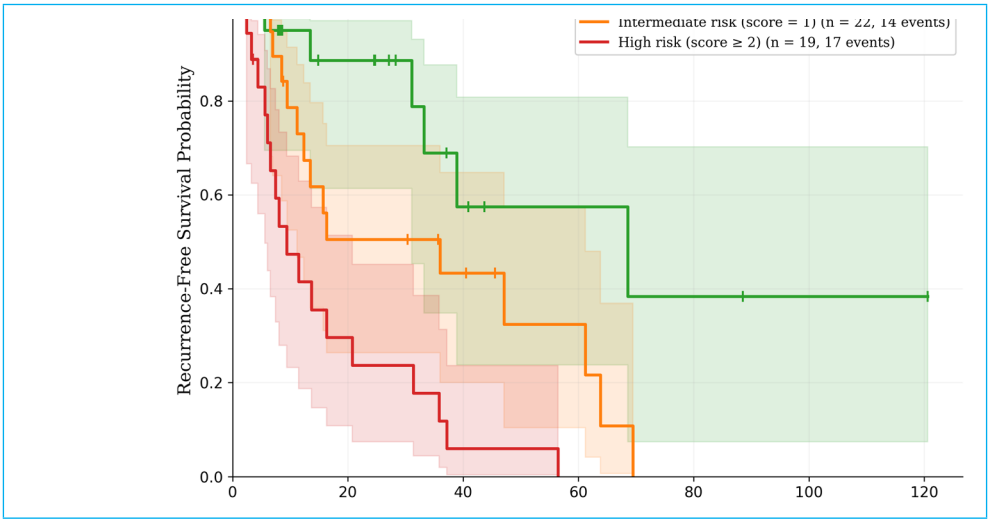


Figure 4. Exploratory risk-stratification analysis: Kaplan–Meier RFS by risk group. A composite risk score was derived from the three independent prognostic factors: sarcomatoid differentiation (+2 points), age ≥60 years (+1 point), and >2 metastatic organ sites (+1 point). Three risk groups were defined: low risk (score=0; n=23; green), intermediate risk (score=1; n=22; orange), and high risk (score ≥2; n=19; red). The three-group log-rank test was highly significant (p<0.001). This score is exploratory and requires external validation.

application. The exploratory risk-stratification Kaplan–Meier curves are presented in Figure 4.

Discussion

In this multicenter retrospective analysis of 81 oligometastatic RCC patients treated with curative-intent local therapy across seven Turkish centers, we identified three independent predictors of recurrence: sarcomatoid differentiation, advancing age, and increasing number of metastatic organ sites. An exploratory risk score derived from these factors separated patients into groups with markedly different RFS trajectories. These findings are hypothesis-generating and add to the limited body of evidence on prognostic factors in this specific clinical context.

Sarcomatoid Differentiation: The Dominant Risk Factor

The most prominent finding is the association of sarcomatoid differentiation with a more than fourfold increase in recurrence risk (HR=4.30; p=0.003). This is biologically plausible given the established aggressive biology of sarcomatoid RCC, which is characterized by high proliferative indices, epithelial-to-mesenchymal transition, and resistance to conventional targeted therapies.[17,18] Kaplan–Meier curves stratified by sarcomatoid differentiation confirmed marked separation (Supplementary Fig. S3; log-rank p<0.001).

Consistent with our findings, a multicenter analysis of the KRoCS database by Choi et al.[19] found that sarcomatoid differentiation was independently associated with worse overall survival (HR=1.62; p<0.001) and with progression during first-line treatment (HR=1.45; p<0.001) among patients with metastatic RCC. The larger hazard ratio in our study (4.30 vs. 1.62) may reflect the specific context of post-curative-therapy recurrence in the oligometastatic setting, although differences in cohort composition, sample size, and treatment era could also contribute.

From a therapeutic perspective, sarcomatoid RCC has shown responsiveness to immune-checkpoint inhibitor combinations. The CheckMate 214 subgroup analysis demonstrated notable response rates with nivolumab plus ipilimumab in sarcomatoid RCC (ORR 60.8% vs. 23.1% with sunitinib).[20,21] These data were generated in the first-line metastatic setting rather than in the adjuvant context and provide background rationale for considering immunotherapy-based approaches in high-risk patients. Whether oligometastatic patients with sarcomatoid features specifically benefit from adjuvant immunotherapy remains an open question that cannot be answered by the present study.

Metastatic Organ Burden

The number of metastatic organ sites emerged as an independent predictor of recurrence (HR=1.31 per additional organ; p=0.028), with each additional involved organ conferring a 31% increase in recurrence risk. This finding highlights the prognostic heterogeneity within the oligometastatic RCC population and supports a dose-response relationship between metastatic burden and recurrence risk.

These results are consistent with published data from Dabestani et al.[10], who reported superior outcomes in single-organ versus multi-organ metastatic RCC following local therapy, and with EAU[4] and ESMO[22] guidelines that emphasize limited metastatic burden as a factor in patient selection for curative-intent approaches. The median number of metastatic organ sites in our cohort was 2 (range 1–6 among 78 evaluable patients; three patients with zero recorded sites likely represent incomplete site-level documentation). This range, when considering patients with the highest burden in the cohort, extends beyond the ≤3–5 lesion threshold commonly cited in earlier oligometastatic definitions, and the broader inclusion may limit direct comparability with studies that employed stricter definitions. The finding nevertheless reinforces the notion that clinical decision-making in this space is driven by the perceived feasibility of achieving a disease-free state rather than by strict numerical boundaries.

Age as a Prognostic Factor

Advancing age was independently associated with recurrence (HR=1.04 per year; p=0.015), corresponding to approximately a 48% increase in recurrence risk per decade. This association may reflect age-related immunosenescence and impaired antitumor immune surveillance[23], higher comorbidity burden that limits the aggressiveness of salvage therapies, or less favorable tumor biology in older patients.

Age has been inconsistently reported as a prognostic factor in metastatic RCC. It is not included in the IMDC model, though it has been identified as significant in selected series.[24] Our finding suggests that in the curative-intent oligometastatic setting—where the goal is durable disease control rather than palliation—the influence of age-related factors on recurrence may be more apparent.

Pathological T Stage and the Proportional Hazards Violation

Pathological T stage violated the proportional hazards assumption (p=0.037), suggesting that its effect on recurrence risk varied over time (Supplementary Fig. S5). Therefore, pT stage was incorporated as a stratification factor in the multivariate model rather than as a conventional covariate.

Non-Significance of IMDC Parameters

A negative finding of note is the lack of statistical significance for conventional IMDC risk factors—hemoglobin, calcium, neutrophil count, LDH, and platelet count—in our oligometastatic cohort. The IMDC model was developed and validated in unselected metastatic RCC populations receiving systemic therapy[15], and our results raise the possibility that its constituent parameters may have limited prognostic utility in the curative-intent oligometastatic setting. This observation aligns with the emerging concept that oligometastatic RCC may represent a biologically distinct entity with prognostic determinants that differ from those of widely disseminated disease.[6,25] The limited sample size and the possibility that laboratory values may have been measured at heterogeneous time points across centers mean that these null findings should be interpreted with caution rather than taken as definitive evidence against the relevance of IMDC parameters in this population.

Exploratory Risk Stratification

The exploratory risk score derived from our multivariate model identified three groups with significantly different recurrence risks (log-rank p<0.001), ranging from 26.1% in the low-risk group to 89.5% in the high-risk group. However, because the score was developed and tested within the same cohort, it requires external validation before broader application.

The relatively small sample size and the use of categorized variables may limit generalizability. Therefore, this score should be regarded as an exploratory tool rather than a model ready for routine clinical use. If validated in independent cohorts, it may help support risk-adapted surveillance strategies following curative-intent local therapy.

OS Interpretation and Endpoint Maturity

Median OS in our cohort was 63.8 months, which exceeds the 22–43-month median OS typically reported for unselected metastatic RCC populations in the targeted therapy era.[15,26] This is consistent with the more favorable prognosis expected in the oligometastatic phenotype. However, the OS estimate is based on only 21 death events in 63 evaluable patients, and the resulting confidence intervals are wide. With additional follow-up, the final OS figure may be materially different. RFS, with 37 events and more complete data, is the more statistically stable endpoint in this study and should be considered the primary basis for the conclusions drawn.

Comparison with World Literature

Our median RFS of 31.4 months falls within the range reported in comparable oligometastatic RCC series. Bianchi et al.[27] reported median progression-free intervals of 12–36 months in oligometastatic cohorts, and the SABR-COMET trial demonstrated improved OS with metastasis-directed therapy in oligometastatic cancers of various histologies.[28]

The predominance of lung (54.3%) and bone (43.8%) metastases in our cohort is consistent with the known meta-

static tropism of RCC.[27] The independent prognostic significance of bone metastasis on univariate analysis (HR=1.99; p=0.035) aligns with published data demonstrating inferior outcomes in bone-predominant metastatic RCC.[29] Kaplan–Meier RFS curves stratified by bone metastasis status are shown in Supplementary Figure S6.

The CARMENA and SURTIME trials have refined our understanding of cytoreductive nephrectomy in the systemic therapy era.[30,31] While these trials focused on synchronous metastatic disease in the targeted therapy setting, the principles of disease burden assessment and patient selection for local therapy are relevant to the oligometastatic context.

Immunotherapy Context

The adjuvant immunotherapy field continues to evolve. KEYNOTE-564 has demonstrated disease-free and OS benefits with adjuvant pembrolizumab in high-risk RCC[14,32], while CheckMate 914[33] and IMmotion010[34] did not show significant benefit for adjuvant nivolumab plus ipilimumab or adjuvant atezolizumab, respectively. Current EAU[4] and ESMO[22] guidelines are incorporating these findings into treatment recommendations for high-risk patients after surgery. Our study identifies prognostic factors for recurrence in the oligometastatic setting and does not evaluate treatment efficacy. Whether the prognostic factors identified here can help select oligometastatic patients who might benefit from adjuvant immunotherapy remains an open question requiring dedicated clinical investigation.

Strengths and Limitations

The strengths of this study include its multicenter design spanning seven institutions, the detailed clinicopathological dataset, rigorous attention to statistical methodology (PH assumption testing, EPV-appropriate model building, pT-stratified analysis), and the identification of biologically plausible prognostic factors in an understudied population.

Several limitations warrant acknowledgment. First, the retrospective design is inherently susceptible to selection bias and unmeasured confounding. The decision to pursue curative-intent local therapy was made by individual treating teams, introducing selection that is difficult to quantify. Second, the sample size of 81 patients limited the power for OS analysis (21 events) and precluded more complex modeling. Third, heterogeneity across the seven participating centers—with contributions ranging from 3 to 22 patients per site, different treatment protocols, pathological reporting practices, and surveillance schedules accumulated across the patient inclusion period (April 2010–October 2022)—may have introduced variability in both predictor ascertainment and outcome measurement. Era effects during this period, including the introduction of immune-checkpoint inhibitors into practice, may also have influenced outcomes. A shared frailty or random-effects model was not employed given the small number of centers and the limited cluster sizes at some sites. Fourth, histological subtypes were not uniformly reported, precluding subtype-specific analyses. Fifth, the absence of central pathology review is a limitation common to multicenter retrospective studies but may be particularly relevant for sarcomatoid differentiation and tumor necrosis, where interobserver variability is well documented. Sixth, missing data—affecting approximately 5–11% of pathological variables and 21% of curative treatment dates—were handled by complete-case analysis, which may introduce bias if the missingness is not random. Seventh, the broad range of metastatic burden in our cohort (up to 6 organ sites and 22 total lesions in some patients) exceeds conventional oligometastatic thresholds and may limit direct comparability with studies using stricter definitions. Eighth, the risk-stratification score was derived and evaluated within the same cohort, precluding any assessment of external validity. Finally, three patients in the database had no recorded metastatic organ sites, likely reflecting data entry inconsistencies, and one patient had a data entry error that produced a negative survival time; these were handled as described in the Methods and Results sections.

Conclusion

In this multicenter study of 81 oligometastatic RCC patients treated with curative-intent local therapy across seven Turkish centers between April 2010 and October 2022, sarcomatoid differentiation (HR=4.30; p=0.003), advancing age (HR=1.04 per year; p=0.015), and the number of metastatic organ sites (HR=1.31; p=0.028) were identified as independent predictors of recurrence on RFS analysis (37 events in 64 evaluable patients). An exploratory composite risk score derived from these three factors separated patients into subgroups with divergent RFS trajectories (p<0.001), although this score has not been externally validated and is not ready for clinical implementation.

These findings may help inform adjuvant treatment discussions and surveillance strategies for oligometastatic RCC, but they should be regarded as hypothesis-generating. Prospective external validation in independent, multi-institutional cohorts is required before integration into clinical practice. The identification of sarcomatoid histology and metastatic organ burden as dominant recurrence predictors in this setting adds to the growing evidence base for individualized risk assessment in oligometastatic RCC.

Disclosures

Ethics Committee Approval: The study was approved by the Necmettin Erbakan University Non-Pharmaceutical and Medical Device Research Ethics Committee (no: 2022/4013, date: 21.10.2022).

Informed Consent: Informed consent was waived due to the retrospective nature of the study by the Ethics Committee.

Conflicts of Interest: The authors declared none.

Funding: The authors declared no funding.

Use of AI for Writing Assistance: The authors declared that no AI tools were used in writing, editing, or proofreading of the manuscript.

Authorship Contributions: Concept – EH, MA; Design – EH, MA; Supervision – MA, UK; Materials – EH, GD, ÇG, NA, MS, UK, NS, OK, TA, APE, İH, MA; Data Collection or Processing: EH, GD, ÇG, NA, MS, UK, OK, TA, APE, İH, MA; Analysis or Interpretation: EH, MA; Literature Search: EH, MA; Writing: EH; Critical Review: GD, ÇG, NA, MS, UK, NS, OK, TA, APE, İH, MA.

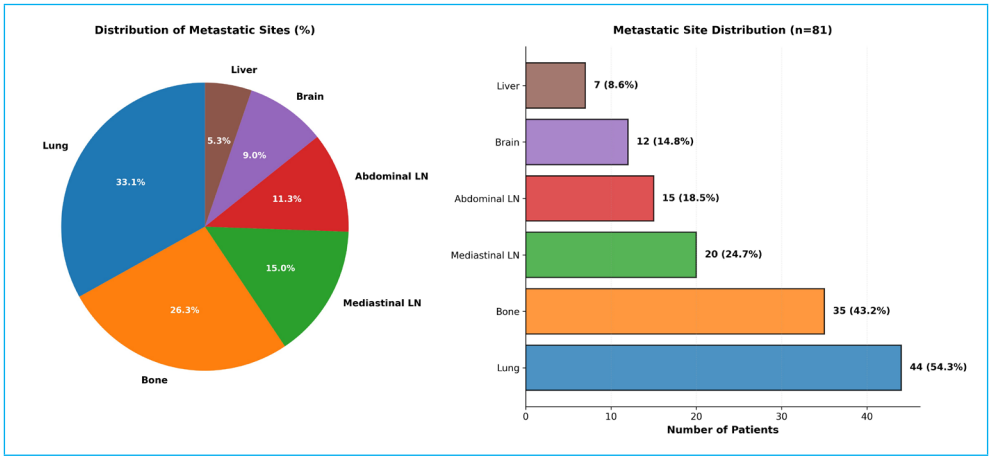
Peer-review: Externally peer-reviewed.

References

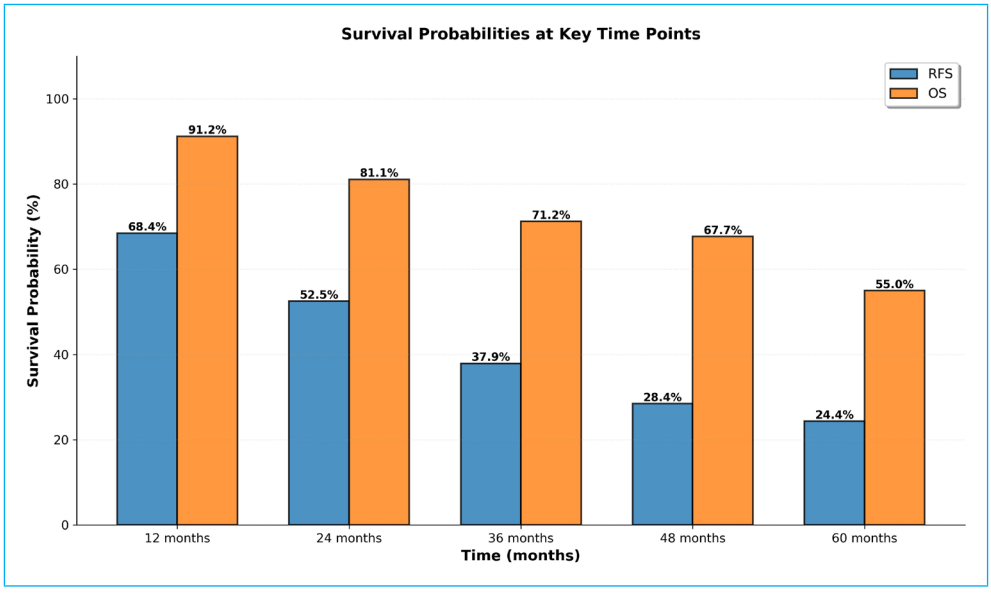
1. Sung H, Filho AM, Laversanne M, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2024: GLOBOCAN estimates of incidence and mortality worldwide for 34 cancers in 186 countries. CA Cancer J Clin 2026;76(4):e70090. [CrossRef]
2. Capitanio U, Bensalah K, Bex A, Boorjian SA, Bray F, Coleman J, et al. Epidemiology of renal cell carcinoma. Eur Urol 2019;75(1):74–84. [CrossRef]
3. Janzen NK, Kim HL, Figlin RA, Belldegrun AS. Surveillance after radical or partial nephrectomy for localized renal cell carcinoma and management of recurrent disease. Urol Clin North Am 2003;30(4):843–52. [CrossRef]
4. Ljungberg B, Albiges L, Abu-Ghanem Y, Bedke J, Capitanio U, Dabestani S, et al. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2022 Update. Eur Urol 2022;82(4):399–410. [CrossRef]
5. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol 1995;13(1):8–10. [CrossRef]
6. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET phase II randomized trial. J Clin Oncol 2020;38(25):2830–8. [CrossRef]
7. Lievens Y, Guckenberger M, Gomez D, Hoyer M, Iyengar P, Kindts I, et al. Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document. Radiother Oncol 2020;148:157–66. [CrossRef]
8. Motzer RJ, Jonasch E, Agarwal N, Alva A, Baine M, Beckermann K, et al. Kidney cancer, version 3.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2022;20(1):71–90. [CrossRef]
9. Alt AL, Boorjian SA, Lohse CM, Costello BA, Leibovich BC, Blute ML. Survival after complete surgical resection of multiple metastases from renal cell carcinoma. Cancer 2011;117(13):2873–82. [CrossRef]
10. Dabestani S, Marconi L, Hofmann F, Stewart F, Lam TB, Canfield SE, et al. Local treatments for metastases of renal cell carcinoma: a systematic review. Lancet Oncol 2014;15(12):e549–61. [CrossRef]
11. Siva S, Louie AV, Warner A, Muacevic A, Gandhidasan S, Ponsky L, et al. Pooled analysis of stereotactic ablative radiotherapy for primary renal cell carcinoma: A report from the International Radiosurgery Oncology Consortium for Kidney (IROCK). Cancer 2018;124(5):934–42. [CrossRef]
12. Hofmann HS, Neef H, Krohe K, Andreev P, Silber RE. Prognostic factors and survival after pulmonary resection of metastatic renal cell carcinoma. Eur Urol 2005;48(1):77–81. [CrossRef]
13. Siva S, Kothari G, Muacevic A, Louie AV, Slotman BJ, Teh BS, et al. Radiotherapy for renal cell carcinoma: renaissance of an overlooked approach. Nat Rev Urol. 2017;14(9):549–63. [CrossRef]
14. Choueiri TK, Tomczak P, Park SH, Venugopal B, Ferguson T, Chang YH, et al; KEYNOTE-564 Investigators. Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma. N Engl J Med 2021;385(8):683–94. [CrossRef]
15. Heng DY, Xie W, Regan MM, Warren MA, Golshayan AR, Sahi C, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol 2009;27(34):5794–9. [CrossRef]
16. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol 2007;165(6):710–8. [CrossRef]
17. Shuch B, Bratslavsky G, Linehan WM, Srinivasan R. Sarcomatoid renal cell carcinoma: a comprehensive review of the biology and current treatment strategies. Oncologist 2012;17(1):46–54. [CrossRef]
18. Blum KA, Gupta S, Tickoo SK, Chan TA, Russo P, Motzer RJ, et al. Sarcomatoid renal cell carcinoma: biology, natural history and management. Nat Rev Urol 2020;17(12):659–78. [CrossRef]
19. Choi J, Bang S, Suh J, Choi CI, Song W, Yuk HD, et al. Survival pattern of metastatic renal cell carcinoma patients according to WHO/ISUP grade: a long-term multi-institutional study. Sci Rep 2024;14(1):4740. [CrossRef]
20. Tannir NM, Signoretti S, Choueiri TK, McDermott DF, Motzer RJ, Flaifel A, et al. Efficacy and safety of nivolumab plus ipilimumab versus sunitinib in first-line treatment of patients with advanced sarcomatoid renal cell carcinoma. Clin Cancer Res 2021;27(1):78–86. [CrossRef]
21. Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, et al; CheckMate 214 Investigators. Nivolumab plus ipilimumab versus sunitinib in advanced

renal-cell carcinoma. N Engl J Med 2018;378(14):1277–90. [CrossRef]
22. Escudier B, Porta C, Schmidinger M, Rioux-Leclercq N, Bex A, Khoo V, et al; ESMO Guidelines Committee. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2019;30(5):706–20. [CrossRef]
23. Pawelec G, Derhovanessian E, Larbi A. Immunosenescence and cancer. Crit Rev Oncol Hematol 2010;75(2):165–72. [CrossRef]
24. Motzer RJ, Bacik J, Schwartz LH, Reuter V, Russo P, Marion S, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. J Clin Oncol 2004;22(3):454–63. [CrossRef]
25. Meagher MF, Mir MC, Minervini A, Kriegmair M, Heck M, Porpiglia F, et al. Proposal for a two-tier re-classification of stage IV/M1 domain of renal cell carcinoma into M1 ("oligometastatic") and M2 ("polymetastatic") subdomains: Analysis of the registry for metastatic renal cell carcinoma (REMARCC). Front Oncol 2023;13:1113246. [CrossRef]
26. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356(2):115–24. [CrossRef]
27. Bianchi M, Sun M, Jeldres C, Shariat SF, Trinh QD, Briganti A, et al. Distribution of metastatic sites in renal cell carcinoma: a population-based analysis. Ann Oncol 2012;23(4):973–80. [CrossRef]
28. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet 2019;393(10185):2051–8. [CrossRef]
29. McKay RR, Kroeger N, Xie W, Lee JL, Knox JJ, Bjarnason GA, et al. Impact of bone and liver metastases on patients with renal cell carcinoma treated with targeted therapy. Eur Urol 2014;65(3):577–84. [CrossRef]
30. Méjean A, Ravaud A, Thezenas S, Colas S, Beauval JB, Bensalah K, et al. Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. N Engl J Med 2018;379(5):417–27. [CrossRef]
31. Bex A, Mulders P, Jewett M, Wagstaff J, van Thienen JV, Blank CU, et al. Comparison of immediate vs deferred cytoreductive nephrectomy in patients with synchronous metastatic renal cell carcinoma receiving sunitinib: The SURTIME randomized clinical trial. JAMA Oncol 2019;5(2):164–70. Erratum in: JAMA Oncol 2019;5(2):271. [CrossRef]
32. Choueiri TK, Tomczak P, Park SH, Venugopal B, Ferguson T, Symeonides SN, et al; KEYNOTE-564 Investigators. Overall survival with adjuvant pembrolizumab in renal-cell carcinoma. N Engl J Med 2024;390(15):1359–71. [CrossRef]
33. Motzer RJ, Russo P, Grünwald V, Tomita Y, Zurawski B, Parikh O, et al. Adjuvant nivolumab plus ipilimumab versus placebo for localised renal cell carcinoma after nephrectomy (CheckMate 914): a double-blind, randomised, phase 3 trial. Lancet 2023;401(10379):821–32. [CrossRef]
34. Pal SK, Uzzo R, Karam JA, Master VA, Donskov F, Suarez C, et al. Adjuvant atezolizumab versus placebo for patients with renal cell carcinoma at increased risk of recurrence following resection (IMmotion010): a multicentre, randomised, double-blind, phase 3 trial. Lancet 2022;400(10358):1103–16. [CrossRef]

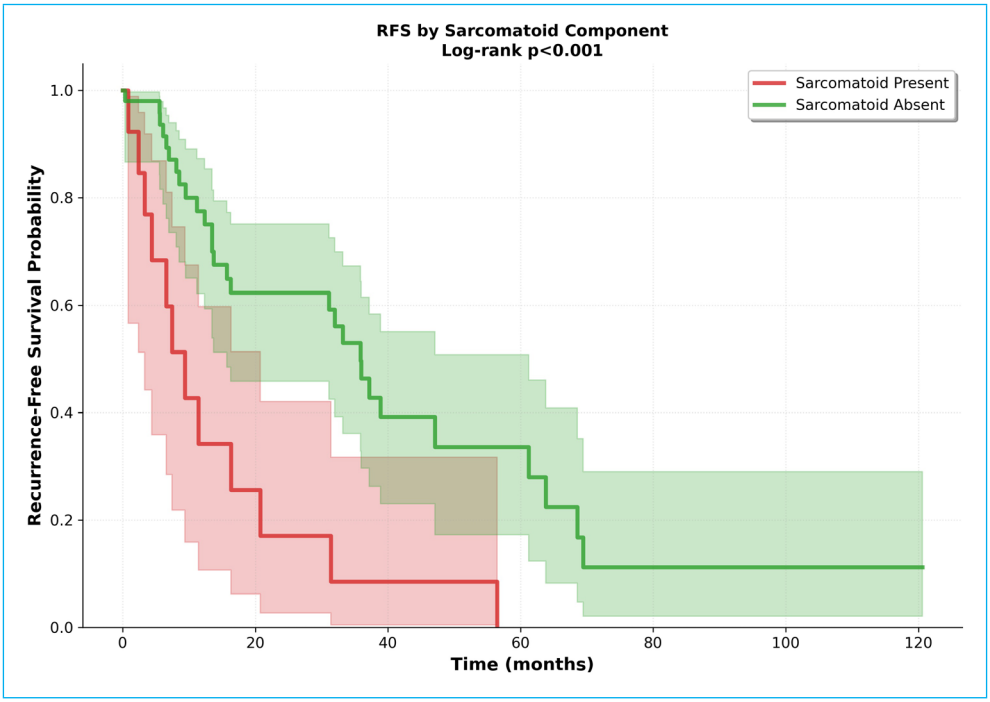
Supplementary Material



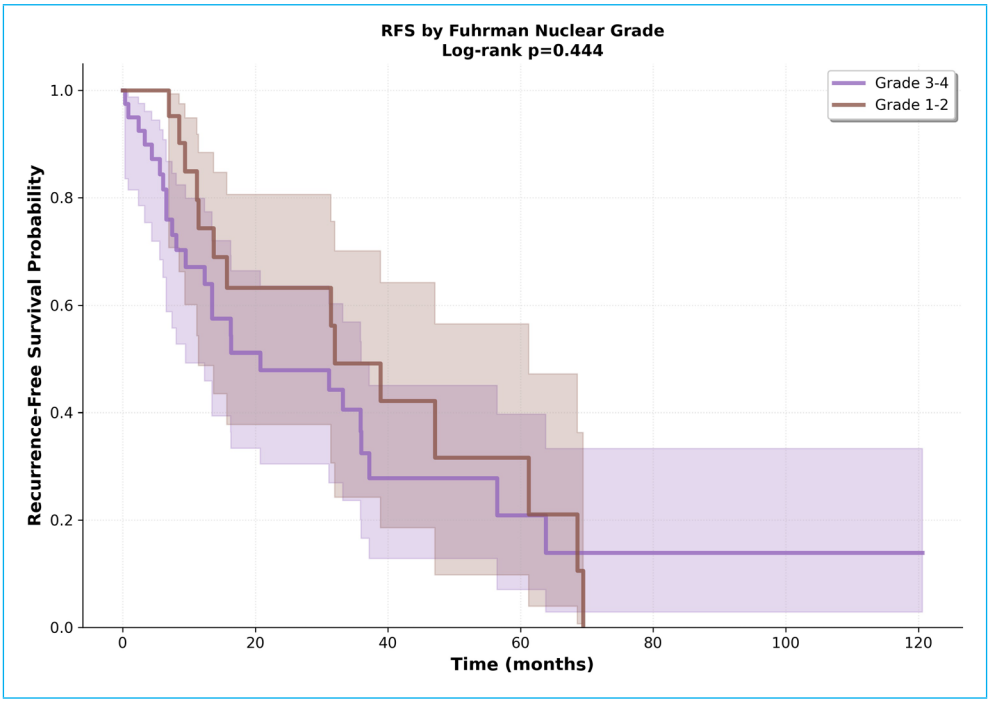
Supplementary Figure S1. Distribution of metastatic sites.
Distribution of metastatic sites in the study cohort (N=81). Left panel: Pie chart showing percentage distribution of metastatic sites. Right panel: Horizontal bar chart showing absolute patient counts with percentages. Most common sites: lung (54.3%), bone (43.8%), mediastinal lymph nodes (24.7%), abdominal lymph nodes (18.5%), brain (14.8%), and liver (8.6%). Patients may have multiple metastatic sites; percentages sum to more than 100%.



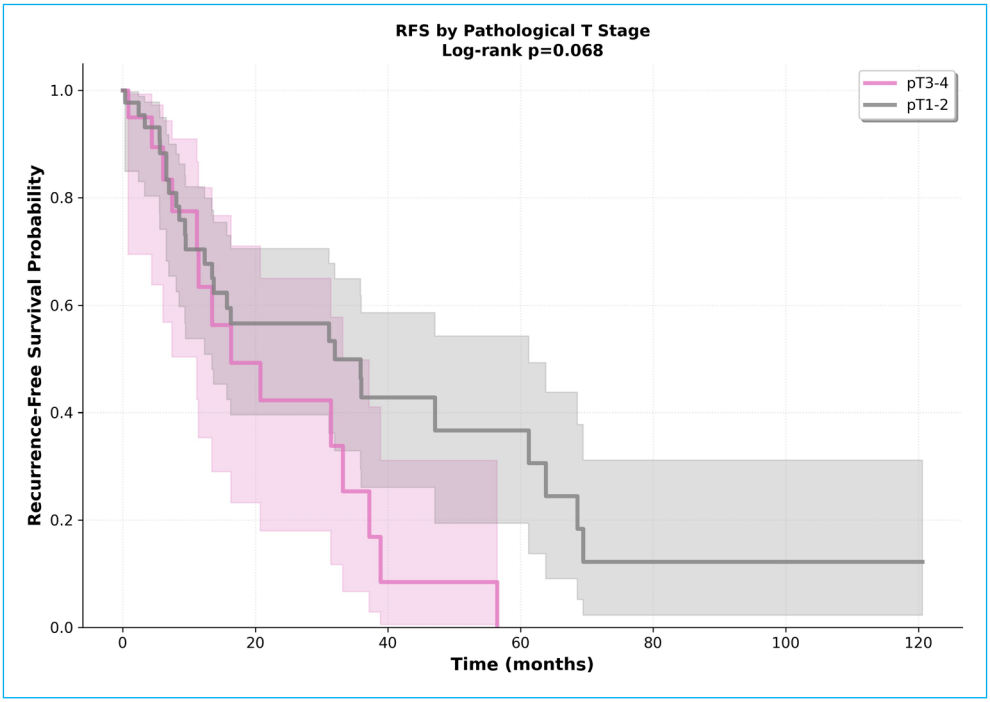
Supplementary Figure S2. Survival probabilities at key time points.
Bar chart showing RFS (blue bars) and OS (orange bars) probabilities at 12, 24, 36, 48, and 60 months. RFS probabilities: 68.4%, 52.5%, 37.9%, 28.4%, and 24.4%. OS probabilities: 91.2%, 81.1%, 71.2%, 67.7%, and 55.0%. OS estimates beyond 36 months are based on a diminishing number of patients at risk and should be interpreted with appropriate caution given the limited number of death events (n=21).



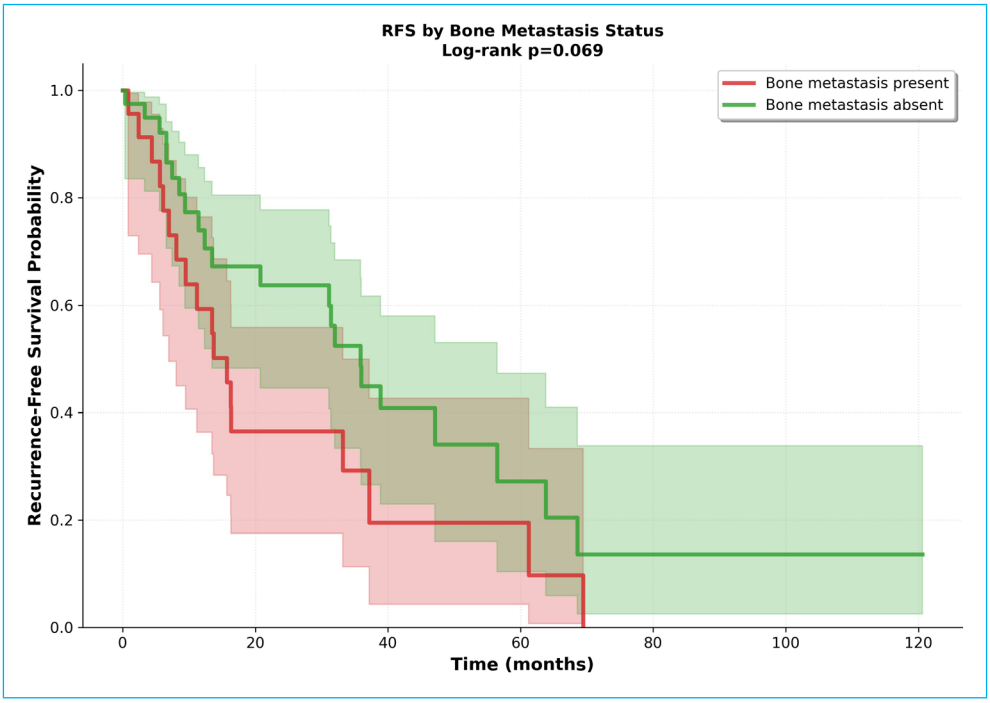
Supplementary Figure S3. RFS by sarcomatoid differentiation.
Kaplan–Meier RFS curves stratified by sarcomatoid differentiation. Patients with sarcomatoid differentiation (red line) showed significantly worse RFS compared to those without (green line). Log-rank p<0.001. Shaded areas represent 95% confidence intervals.



Supplementary Figure S4. RFS by Fuhrman grade.
Kaplan–Meier RFS curves stratified by Fuhrman nuclear grade. Grade 3–4 (purple line) vs. Grade 1–2 (brown line). Log-rank p=0.444. No statistically significant difference was observed between grade groups.



Supplementary Figure S5. RFS by pT stage.
Kaplan–Meier RFS curves stratified by pathological T stage. pT3–4 (pink line) vs. pT1–2 (gray line). Log-rank p=0.068. Borderline significance was observed, with pT3–4 tumors showing a trend toward worse RFS.



Supplementary Figure S6. RFS by bone metastasis.
Kaplan–Meier RFS curves stratified by bone metastasis status. Bone metastasis present (red line) vs. absent (green line). Log-rank p=0.069. Bone metastasis was significantly associated with shorter RFS in univariate Cox analysis (HR=1.99; 95% CI 1.05–3.77; p=0.035).