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Impact of rhabdoid differentiation on postoperative outcome for patients with N0M0 renal cell carcinoma

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Abstract

Background and Objective: We assessed the aggressiveness of localized renal cell carcinoma (N0M0 RCC) with rhabdoid differentiation (RD) after partial or radical nephrectomy.

Methods: A total of 604 patients with N0M0 RCC who had undergone partial or radical nephrectomy at a single institution were included in this study. Clinicopathological and outcome data on recurrence-free survival (RFS), cancer-specific survival (CSS), and time to recurrence (TTR) were analyzed using Kaplan-Meier methods, log-rank test, univariate and multivariable Cox proportional hazard models, and concordance index. We also evaluated the RFS and CSS in a propensity score-matched cohort to reduce inherent differences. Among the 604 patients, RD was identified in RCC specimens from 24 patients.

Results: At the median postoperative follow-up period of 53 months, 58 patients (12 with RD) showed recurrence and 26 patients (7 with RD) had died from RCC. Multivariate analyses showed that RD was an independent risk factor of RFS (hazard ratio 2.81; $P = 0.0266$) and CSS (hazard ratio 5.18; $P = 0.00182$). By RD adding to standard risk factors, the concordance indices for RFS and CSS increased 0.77 to 0.79, and 0.76 to 0.79, respectively. Subgroup analysis showed that the presence of RD in RCC specimens was more important for predicting poor RFS and CSS in the early pathological tumor category (≤pT2) subgroup compared to in the advanced tumor category (≥pT3) subgroup. Patients with RD showed a significantly shorter TTR than patients with RCC without RD (7.5 vs. 18 months: $P = 0.0150$). The propensity score-matched cohort included 24 patients with RD and 24 without RD, of which patients RD showed significantly shorter RFS than those without RD ($P = 0.0026$).

Conclusions: In summary, the aggressiveness of N0M0 RCC with RD increased the risk of postoperative recurrence, particularly in the early pathological stage. The short TTR also demonstrated the aggressiveness of RCC with RD.

Keywords: Renal cell carcinoma; Localized renal cell carcinoma; Rhabdoid differentiation; Propensity score analysis; Time to recurrence

1. Introduction

In localized or locally advanced renal cell carcinoma, surgeries, such as partial or radical nephrectomy result in disease recurrence in 10% to 30% of patients [1,2]. Early detection of recurrence is crucial because metastatic renal cell carcinoma (RCC) can be treated to achieve a complete response using targeted therapy [3] or can be cured by resection of the metastasis [4] if the metastatic tumor has a low tumor burden. In 2012, to predict RCC prognosis from pathological findings, the International Society of Urological Pathology (ISUP) recommended potential prognostic parameters for RCC, including tumor morphotype, sarcomatoid differentiation (SD)/rhabdoid differentiation (RD), tumor necrosis, grading, and microvascular invasion (MVI) [5].

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Among these parameters, RCC with RD generally takes an aggressive course, with rapid progression and poor prognosis, and RCCs with rhabdoid cells are classified by the ISUP as grade 4 tumors [5]. The rhabdoid phenotype was originally identified in pediatric rhabdoid tumors of the kidney, characterized by biallelic genetic inactivation of the *SMARCB1/INI1* tumor suppressor gene and immunohistochemical loss of *SMARCB1/INI1* [6]. In comparison, although its morphological features resemble those of pediatric rhabdoid tumors, RD arising in adult RCC differs in its ultrastructural features and immunophenotype; particularly, *SMARCB1/INI1* expression is positive in rhabdoid cells in adult RCC [5,7]. Adult RCC with RD is rare, with an incidence rate of 1.4% to 7.4% in a relatively large reported series [8−11]. The presence of RD is associated with adverse pathological findings, such as higher nuclear grade, pathological stage, and extrarenal extension [10]. Furthermore, its relationship with a poor clinical prognosis was recently reported in several large studies [12,13]. However, these studies included patients with lymph node involvement or distant metastasis, and only analyzed cancer-related death; no studies have evaluated the impact of RD on postoperative recurrence in N0M0 RCC (localized and locally advanced RCC, excluding cases with pathologically proven lymph node involvement). We aimed to clarify the aggressiveness of N0M0 RCC with RD after complete resection. Specifically, we determined its aggressiveness by evaluating the immunohistochemical findings of primary sites, recurrence-free and cancer-specific survival (CFS and CSS) analyzed using a propensity score-matched cohort and an entire cohort, and time to recurrence (TTR) after complete resection, which is a known clinical indicator predicting a poor outcome of localized RCC [14,15]. Focusing strictly on N0M0 RCC, we validated the role of RD in RCC as a risk factor of postoperative recurrence.

2. Materials and methods

2.1. Patients

The present study included 604 patients who had been treated by partial or radical nephrectomy for N0M0 RCC between 2004 and 2015 at the Department of Urology of Tokai University Hospital and who had been observed for more than 3 months after surgery. Patients' clinicopathological data and postoperative outcome were retrospectively analyzed using their medical records. Patients with simultaneous distant metastasis at the time of surgery or patients with clinically suspected (regional lymph node diameter >5 mm) lymph node involvement or pathologically proven lymph node involvement (pN1) after surgery were excluded. Postoperative recurrence was assessed by chest-abdominal computed tomography or chest X-ray and abdominal ultrasound every 3 to 6 months for 2 years following surgery and every 6 to 12 months thereafter. Occasionally, recurrence was detected based on symptoms that occurred prior to regular imaging. The study design and protocol were approved by Tokai University Institutional Review Board.

2.2. Pathological examinations

A single pathologist (C.I.) blinded to clinical outcomes performed pathological examinations of all slides of patients based on the 2016 WHO classification and the 7th edition of the tumor-node-metastasis staging system [16]. All equivocal cases were reviewed by another pathologist (H.K.) and confirmed by discussion. Maximum tumor diameter, histological subtype, pathological T category, MVI, SD, and RD were examined. SD and RD in RCC were diagnosed by microscopic examination according to previously reported definitions [10,17]. Briefly, SD was represented by spindle cells that histologically appeared as sarcoma. In contrast, RD was represented by large epithelioid cells with vesicular nuclei, prominent nucleoli, and central eosinophilic intracytoplasmic inclusions. Immunohistochemical analyses were performed on 4-μm sections of formalin-fixed, paraffin-embedded samples. Automated staining was performed using a BenchMark ULTRA system (Roche/Ventana Biosystems, Basel, Switzerland) or Leica Bond MAX Autostainer (Leica Biosystems, Wetzlar, Germany) according to the manufacturer's protocols. We used the following primary antibodies: anti-E-cadherin (Clone 36B5, Leica Biosystems, at 1:50 dilution, Newcastle, Newcastle Upon Tyne, UK), anti-Vimentin (Clone V9, Roche Diagnostics, prediluted), and anti-INI1 (Clone 25/BAF47, BD Biosciences, San Jose, CA). Membranous staining indicated E-cadherin positivity, cytoplasmic staining indicated vimentin positivity, and nuclear staining indicated INI1 positivity. We used E-cadherin and vimentin to assess epithelial-mesenchymal transition (EMT) markers. We compared the RD component and clear cell component in each patient. INI1 was used to distinguish rhabdoid tumors which typically arise in infants or other rare histological subtypes.

2.3. Statistical analyses

To compare the characteristics of the patients with and without RD, Fisher's exact and Chi-square tests were used for qualitative variables, and the Mann-Whitney *U* test was used for quantitative variables. RFS was defined as the time from the day of surgery until the detection of recurrence. The CSS was defined as the time from the day of surgery until death from RCC. Data from patients who were alive without recurrence at the last evaluation, or who died of other causes, were censored. RFS and CSS for clinicopathological factors were calculated according to the Kaplan-Meier curve and compared using the log-rank test. To reduce inherent differences and selection biases, we performed analyses using 2 cohorts to determine clinicopathological risk factors associated with poor clinical outcome: an entire cohort comprising 604 patients and an adjusted cohort matched by propensity score comprising 48 patients.

Among the entire cohort, clinicopathological factors were as follows: age, sex, nephrectomy type, histological subtype, pT category, MVI, SD, and RD. We excluded ISUP nuclear grade from survival analysis because ISUP grade 4 was a high intercorrelation factor of RD. Univariate and multivariate analyses were performed using a Cox proportional hazards model. Uno's concordance index (C-index) was calculated to discriminate the predictive accuracy for postoperative outcomes between a model consisting of standard risk factors and with RD added to the same model [18]. The C-index ranges from 0 to 1.0, with 1.0 indicating perfect predictive models and 0.5 indicating random or no discrimination. TTR between the 2 groups divided by clinicopathological factors was compared using Wilcoxon rank-sum test. To create a cohort adjusted for patients and disease characteristics, the propensity score was calculated using a multivariate logistic regression model including the following 6 factors: age, sex, maximum tumor diameter, histological subtype, pT category, and MVI. Patients without RD were matched to those with RD by propensity score-matching according to the nearest neighbor in a 1:1 manner. P values < 0.05 were considered statistically significant. All statistical analyses were performed with JMP version 12.0.1 (SAS Institute, Cary, NC) and with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics [19].

3. Results

3.1. Patient characteristics

Clinicopathological data of all 604 patients and propensity score-matched cohort of 48 patients, each divided into 2 groups: with and without RD, are summarized in Tables 1 and 2. Overall, the number of RCC patients with and without RD was 24 (4%) and 580 (96%) patients, respectively. All RCC cases with RD underwent radical nephrectomy and showed the clear cell subtype. Patients with RD had, a larger tumor diameter, a higher pT ratio (≥pT3) (41.7% vs. 8.1%), MVI positivity (54.2% vs. 16.6%), and SD positivity (37.5% vs. 0.86%) compared to patients without RD. The median postoperative follow-up period was 53 months (range, 3−141). The matched cohort included 24 patients with RD (50%) and 24 without RD (50%), and the clinicopathological characteristics of the 2 groups did not differ. The median postoperative follow-up period was 30 months (range, 3−123).

3.2. Results of immunohistochemical staining of RCC with rhabdoid differentiation

E-Cadherin was stained positive in one case (4.2%) in the RD component and 22 cases (91.7%) in the clear cell component. Vimentin cytoplasmic staining was positive in 24 cases (100%) in RD component and 1 case (4.2%) in clear cell component which was an eosinophilic variant of clear cell RCC. INI1 was positive in all cases with both RD and clear cell components. Table 3 shows the results of immunohistochemical staining for 24 patients with RD and Fig. 1 shows E-cadherin, vimentin, and INI1 staining patterns in cells with clear cell and rhabdoid cell components.

3.3. Survival analysis of RFS and CSS using the matched 48 cohort after propensity score calculation

Fourteen patients (12 with RD, and 2 without RD) showed recurrence and 9 patients (7 with RD, and 2 without RD) died from RCC during the follow-up. The patients with RD showed statistically significant shorter RFS than patients without RD ($P = 0.0026$), while there was no significant difference in CSS between the 2 groups (Fig. 2). The 5-year RFS rates were 41.3% and 91.3%, while the 5-year CSS rates were 64.1% and 82.0% in patients with and without RD, respectively (Fig. 2).

3.4. Cox proportional hazards regression model analysis of clinicopathological factors affecting RFS and CSS

Among all 604 patients, 58 (12 with RD, and 46 without) showed recurrence, including 3 patients with local recurrence and the other 55 patients with distant metastasis. Finally, 26 patients (7 with RD, and 19 without) died from RCC during the follow-up. Among the clinicopathological factors assessed by the Cox proportional hazards regression model, a higher age, radical nephrectomy, pT (≥pT3), the presence of MVI, SD, and RD were associated with RFS, while a higher age, radical nephrectomy, pT (≥pT3), the presence of MVI, SD, and RD were associated with CSS according to univariate analysis. Multivariate analysis for RFS identified radical nephrectomy, pT (≥pT3), the presence of MVI, and the presence of RD as independent prognostic factors associated with postoperative recurrence (Table 4). Multivariate analysis for CSS identified a higher age, the presence of MVI, and RD as independent prognostic factors associated with death from RCC (Table 5). From the results of univariate and multivariate analysis for RFS and CSS, the pT category and MVI were included in the standard risk model. The C-index for RFS using the standard risk model (pT category and MVI) and RD risk model (RD, pT category, and MVI) were 0.77 (confidence interval [CI]: 0.69−0.85) and 0.79 (CI: 0.71−0.86), respectively. The C-index for CSS using the standard risk model and RD risk model was 0.76 (CI: 0.63−0.88) and 0.79 (CI: 0.66−0.91), respectively.

3.5. Subgroup analyses in patients with early (≤pT2) and advanced (pT3) pathological tumor categories

In the entire N0M0 RCC cohort, we identified the presence of RD as an independent risk factor for RFS

Table 1
Clinicopathological characteristics of RCC with and without RD

Variable	The entire cohort ($n = 604$)		P
	With RD ($n = 24$)	Without RD ($n = 580$)	
Age (y), median (range)	62.5 (49−82)	63 (22−87)	0.090
Sex			0.230
Female	9	146	
Male	15	434	
Nephrectomy			<0.001
Partial	0	209	
Radical	24	371	
N category			0.277
pN0	2	24	
NX	22	556	
Histological subtype			0.022
Clear cell	24	476	
Nonclear	0	104	
Papillary	0	39	
Chromophobe	0	36	
ACD-associated	0	12	
Multilocular cystic renal neoplasm of low malignant potential	0	9	
Clear papillary	0	5	
Collecting duct carcinoma	0	1	
mucinous tubular and spindle cell carcinoma	0	1	
Unclassified	0	1	
Tumor size (mm), median (range)	65 (29−150)	30 (9−250)	<0.001
Pathological T category			<0.001
T1	10	507	
T2	4	26	
T3	10	46	
T4	0	1	
ISUP grade			<0.001
1	0	9	
2	0	324	
3	0	236	
4	24	11	
MVI			<0.001
Absence	11	484	
Presence	13	96	
Sarcomatoid differentiation			<0.001
Presence	9	5	
Absence	15	575	

ACD = acquired cystic disease; MVI = microvascular invasion; RCC = renal cell carcinoma; RD = rhabdoid differentiation.

and CSS. Subsequent subgroup analysis of early (≤pT2) and advanced (≥pT3) pathological tumor categories was performed for RFS and CSS. Fig. 3 shows the Kaplan-Meier curves of RFS and CSS divided into with and without RD in the early pT category subgroup. In this subgroup, patients with RD showed significantly poor RFS and CSS using the log-rank test (both P values <0.0001). The 5-year RFS and CSS rate was 49.1% and 83.6% in patients with RD ($n = 14$), and 94.0% and 98.7% in patients without RD ($n = 533$), respectively. In contrast, there was no significant difference in RFS and CSS between patients with and without RD in the advanced pT category subgroup ($P = 0.257$ and $P = 0.134$, respectively).

3.6. Analysis of the impact of clinical and pathological factors on TTR

The median TTR of RCC with and without RD was 7.5 and 18 months, respectively. The median TTR of tumors ≤pT2 and tumors ≥pT3 was 23 and 9 months, respectively. TTR for patients with RD and with tumors ≥pT3 was significantly shorter ($P = 0.0150$ and $P = 0.0152$, respectively; Table 6, and Fig. 4).

Table 2
Clinicopathological characteristics of the propensity-matched cohort for RCC with and without RD

Variable	The propensity-matched cohort ($n = 48$)		P
	With RD ($n = 24$)	Without RD ($n = 24$)	
Age (y), median (range)	62.5 (49−82)	72.0 (46−79)	0.409
Sex			1.000
Female	9	11	
Male	15	13	
Histological subtype			1.000
Clear cell	24	24	
Nonclear	0	0	
Tumor size (mm), median (range)	62.5 (29−150)	70.0 (25−120)	0.926
Pathological T category			0.743
T1	10	10	
T2	4	6	
T3	10	7	
T4	0	1	
MVI			1.000
Absence	11	10	
Presence	13	14	

MVI = microvascular invasion; RCC = renal cell carcinoma; RD = rhabdoid differentiation.

4. Discussion

RD in RCC is known as a risk factor of aggressive behavior since Gökden et al. first reported the detailed clinical and pathological features of this disease entity [10]. Moreover, RD was recommended as a poor prognostic factor of RCC and was classified as an ISUP grade 4 [5]. Recent large studies of patients with RCC with RD reported both the clinical significance of the presence of RD in RCC and poor CSS and overall survival [12,13]. The presence of RD in RCC is associated poor clinical outcomes; however, the cohorts for these studies showed heterogeneity as patients with lymph node involvement or distant metastasis at surgery were included, and these studies did not evaluate the impact of RD on RFS in N0M0 RCC. Therefore, it is difficult to determine the prognostic value of the presence of RD for postoperative recurrence in N0M0 RCC based on previous reports. Hence, we evaluated RFS and CSS of N0M0 RCC after complete resection.

The results of survival analyses showed that RCC with RD was significantly associated with poor RFS in the propensity score-matched cohort. Multivariate analysis using the Cox proportional hazards regression model revealed RD and MVI as independent risk factors for both RFS and CSS in the entire cohort. The increasing value of the C-index for RFS and CSS after adding RD to the standard risk factors improved the predictive accuracy. Furthermore, we identified an association between poor RFS and CSS and the presence of RD in the early pT category subgroup, but not in the advanced pT category subgroup. These findings suggest that the presence of RD in N0M0 RCC is a reliable pathological predictor of poor clinical outcomes after complete resection, particularly in early pT category tumors.

TTR, as an indicator of poor CSS in localized RCC, has been reported in several studies [18,19]. The most recent large study on TTR after complete resection showed that shorter TTR was significantly associated with an increased risk of cancer-specific mortality [20]. It is well known that patients with late recurrence have better prognosis than those with early recurrence [2,21]. Based on the above reports, we considered TTR after complete resection to be a useful indicator of aggressiveness, and thus analyzed the TTR in N0M0 RCC with or without RD. Among the 58 postoperative patients with recurrence, patients with RD showed a significantly shorter TTR than patients without RD (7.5 vs. 18 months, respectively; $P = 0.0150$). This

Table 3
Immunohistochemical findings of E-cadherin, vimentin, and INI1 in RCC with RD

Immunohistochemical staining	Positivity of rhabdoid component (%)	Positivity of clear cell component (%)
E-cadherin		
membranous staining	1/24 (4.2)	22/24 (91.7)
NA	0	1
Vimentin		
cytoplasmic staining	24/24 (100)	1[a]/24 (4.2)
NA	0	1
INI1		
nuclear staining	24/24 (100)	24/24 (100)

NA = not available or poor staining.
[a] eosinophilic variant.

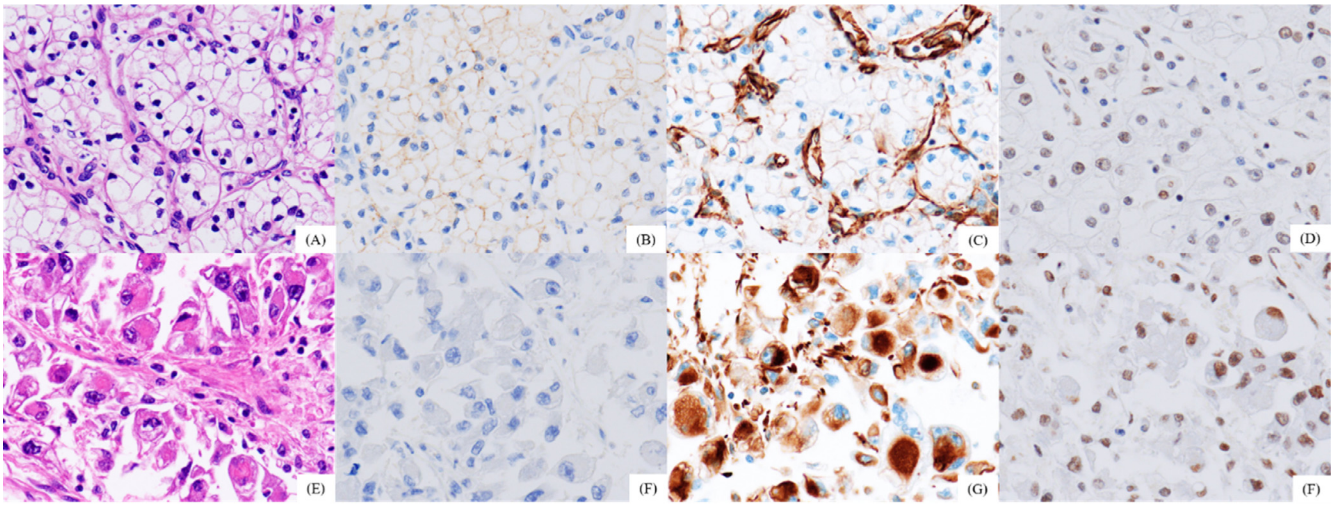

Fig. 1. Representative findings of clear cell RCC without RD; A, Hematoxylin-eosin (HE) staining. B, Membranous E-cadherin expression. C, Membranous vimentin expression. D, Nuclear INI1 expression. E, Representative findings of RCC with RD regarding HE staining. F, E-cadherin loss of expression. G, Cytoplasmic vimentin expression. H, Nuclear INI1 expression. All images are at 40× magnification.

result suggests that patients with RD have a high risk of early recurrence, resulting in poor prognosis, suggesting that patients with RD should be closely observed and considered for postoperative adjuvant therapy [22]. In this study, we also evaluated the impact of the presence of SD, which is an adverse differentiation finding and an adverse prognostic factor for RD, on postoperative recurrence and cancer-related death. Kara et al. [23] evaluated the impact of RD and SD on CSS in 264 patients with grade 4 RCC and found that SD was associated with worse CSS, while RD was not. In the present study, SD was not a significant risk factor for either RFS or CSS. This may be because of the different backgrounds of patients. Our cohort included all ISUP grades and was composed of 90.6% of patients with early pT category tumors, while the previous study cohort included limited grade 4 RCC and was composed of 87.1% of patients with advanced pT category tumors. A study conducted in a similar background (74.1% of patients with advanced pT category tumors) [13] reported the same results as Kara et al. [23]. Differences in the background may have affected the results. In fact, our subgroup analysis of the early and advanced pT category tumors showed that RD was associated with a significantly worse RFS and CSS in only the early subgroup. The other reason may be our small sample size of patients with RD and SD compared to those in previous studies. Increasing the number of patients

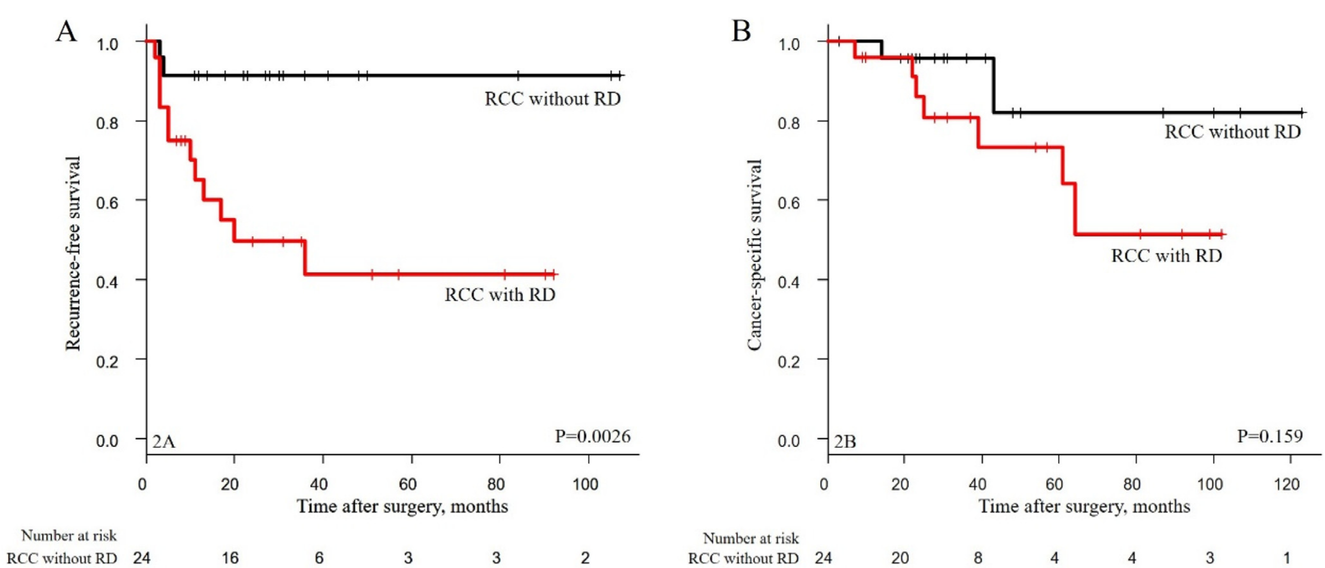

Fig. 2. A, Recurrence-free and B, cancer-specific survival of the patients with N0M0 renal cell cancer in the propensity score-matched cohort comprising 24 patients with rhabdoid differentiation (RD) and 24 without RD.

Table 4
Univariate and multivariate analyses of variables associated with RFS from RCC

Variables	Univariate analysis Risk ratio (95% CI)	*P* value	Multivariate analysis Risk ratio (95% CI)	*P* value
Age	1.03 (1.01−1.06)	0.0109	1.01 (0.99−1.04)	0.2691
Sex				
Female vs. Male	0.88 (0.50−1.60)	0.6562	1.27 (0.72−2.36)	0.4275
Nephrectomy				
Partial vs. Radical	9.27 (3.42−38.0)	<0.0001	3.52 (1.20−15.0)	0.0425
Histological subtype				
Clear vs. Nonclear	0.92 (0.42−1.79)	0.8231	1.38 (0.62−2.78)	0.3983
pT category				
≤pT2 vs. ≥pT3	11.8 (6.98−20.0)	<0.0001	3.05 (1.58−5.97)	0.0010
MVI				
Absence vs. Presence	9.62 (5.68−16.7)	<0.0001	3.84 (1.96−7.55)	< 0.0001
Sarcomatoid differentiation				
without vs. with	9.99 (4.37−20.0)	<0.0001	1.09 (0.38−3.10)	0.8729
Rhabdoid differentiation				
without vs. with	10.5 (5.29−19.3)	<0.0001	2.81 (1.05−6.58)	0.0266

MVI = microvascular invasion; RCC = renal cell carcinoma; RFS = recurrence-free survival.

with RD and SD in the study cohort may affect the results on the impact of the presence of SD on postoperative RFS and CSS.

Vimentin is an EMT marker that has been evaluated in the rhabdoid component and shows a highly positive immunoreaction [8,9,11]. Vimentin staining is characteristically localized in the eosinophilic globular intracytoplasmic body of rhabdoid cells (Fig. 1G). The positive vimentin rate in our group with RD was 100%. Few studies have evaluated E-cadherin immunoactivity in the rhabdoid component [24]. In our study, E-cadherin was positive in 22 cases (91.7%) with a clear component, while one case (4.2%) was positive for a rhabdoid component. The high positive immunoreaction rate of vimentin and high negative rate of E-cadherin in the rhabdoid component indicate EMT and the poor prognosis of RCC [25,26]. These immunoactivity patterns illustrate the aggressiveness of RD. The INI1 protein is a subunit of SWI/SNF chromatin remodeling complexes, which play a role in remodeling nucleosomes and modulating transcription [27]. Loss of INI1 expression is associated with malignant rhabdoid kidney tumor in pediatric pathology, renal medullary carcinoma, or renal carcinoma with Xp11.2 translocations [28−30]. In the present rhabdoid series, nuclear stains for INI1 were 100% positive. This result showed that RCC with RD in our cohort was a

Table 5
Univariate and multivariate analyses of variables associated with CSS from RCC

Variables	Univariate analysis Risk ratio (95% CI)	*P* value	Multivariate analysis Risk ratio (95% CI)	*P* value
Age	1.07 (1.02−1.11)	0.0026	1.05 (1.01−1.10)	0.0141
Sex				
Female vs. Male	0.88 (0.39−2.25)	0.7693	1.44 (0.60−3.88)	0.4332
Nephrectomy				
Partial vs. Radical	5.10 (1.51−31.8)	0.0057	1.41 (0.34−9.52)	0.6687
Histological subtype				
Clear vs. Nonclear	1.25 (0.42−3.07)	0.6626	2.53 (0.79−6.94)	0.0867
pT category				
≤pT2 vs. ≥pT3	10.5 (4.83−23.0)	<0.0001	2.20 (0.83−6.00)	0.1143
MVI				
Absence vs. Presence	10.7 (4.82−26.2)	<0.0001	5.70 (1.99−17.1)	0.0013
Sarcomatoid differentiation				
without vs. with	11.9 (3.93−29.6)	0.0001	0.88 (0.20−4.08)	0.8706
Rhabdoid differentiation				
without vs. with	13.5 (5.22−31.5)	<0.0001	5.18 (1.16−18.3)	0.0182

CSS = cancer-specific survival; MVI = microvascular invasion; RCC = renal cell carcinoma.

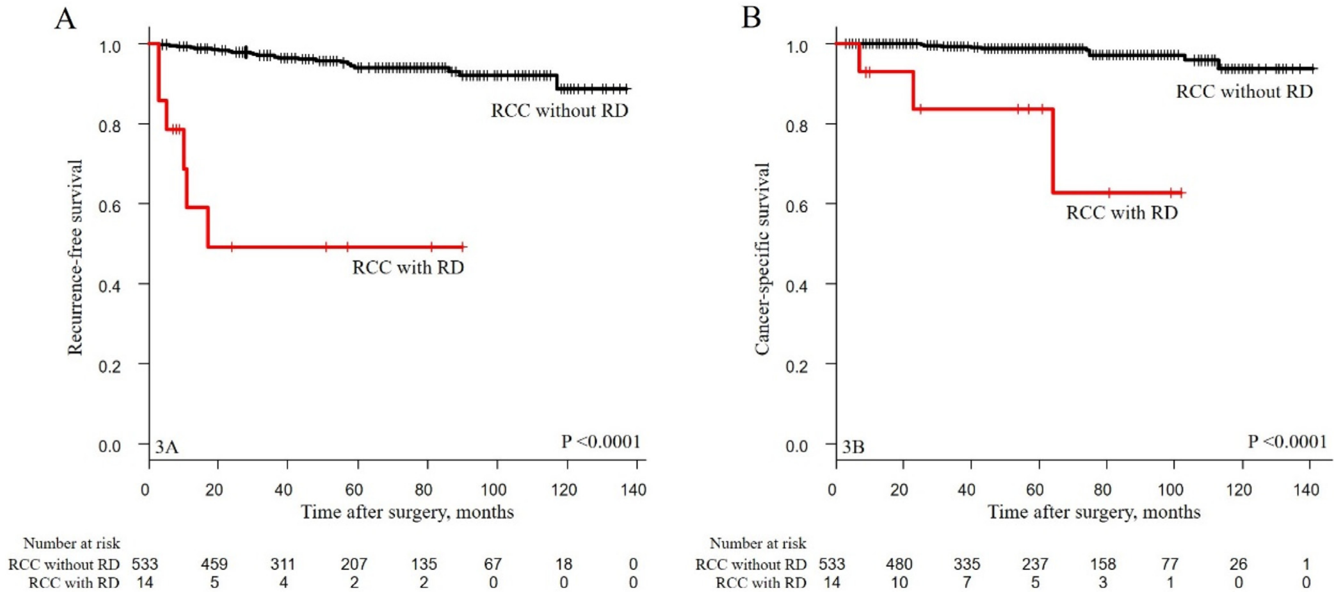

Fig. 3. A, Recurrence-free and B, cancer-specific survival of patients with N0M0 renal cell cancer with or without rhabdoid differentiation in the early pathological tumor category (≤pT2) subgroup.

Table 6
Comparison of time to recurrence after curative surgery using clinicopathological factors

Variables	Time to recurrence (month) median (average)	*P* value
Age (y)		
≤63	11 (24.0)	
>63	19 (25.2)	0.4134
Sex		
Female	8.5 (21.6)	
Male	18 (25.8)	0.1532
Site		
Left	13 (25.2)	
Right	18 (24.1)	0.3875
Nephrectomy		
Partial	30 (26.3)	
Radical	13 (24.6)	0.6477
Histological subtype		
Clear	13 (24.6)	
Nonclear	18 (24.8)	0.3332
pT category		
≤pT2	23 (31.5)	
≥pT3	9 (16.9)	0.0152
MVI		
Absence	20 (28.2)	
Presence	10 (22.6)	0.1471
Sarcomatoid differentiation		
without	16.5 (26.3)	
with	12 (14.3)	0.3847
Rhabdoid differentiation		
without	18 (28.3)	
with	7.5 (10.7)	0.0150

MVI = microvascular invasion.

phenotypic feature differing from malignant rhabdoid tumors arising in pediatric kidney, medullary carcinoma, and renal carcinoma with Xp11.2 translocations [30].

This is the first study to evaluate the clinical impact of RD on clinical outcome in N0M0 RCC. Several previous studies have assessed the impact of RCC with RD on the CSS or OS, although nearly all included patients with lymph node involvement or distant metastasis. Therefore, it was not possible to assess RFS after complete resection or the TTR, which is a novel indicator reflecting the rapidity of disease progression, and provide the appropriate follow-up timing and suggest adjuvant therapies, such as targeted therapy, in the postoperative period [22]. Poor RFS, CSS, and shorter TTR, all of which reflect clinical aggressiveness, were observed in N0M0 RCC with RD in both the entire and matched cohorts. Although the frequency of the occurrence of RD in N0M0 RCC is very low, RD is a strong risk factor of progressive disease, such as early recurrence and rapid progression to life-threatening disease. The results of our study may contribute to more appropriate management of N0M0 RCC and improve survival outcomes.

The limitations of our study were its retrospective design and unevenness of the cases investigated. To strengthen the reliability of the results, external validation in other cohorts or prospective multicenter studies should be performed. The present study did not include information on clinical variables affecting prognosis, such as smoking and obesity during analysis. Additionally, to more accurately describe the aggressiveness of RCC with RD, studies of treatments for patients with recurrence after surgery are needed to predict the effectiveness of therapeutic agents in RCC with RD.

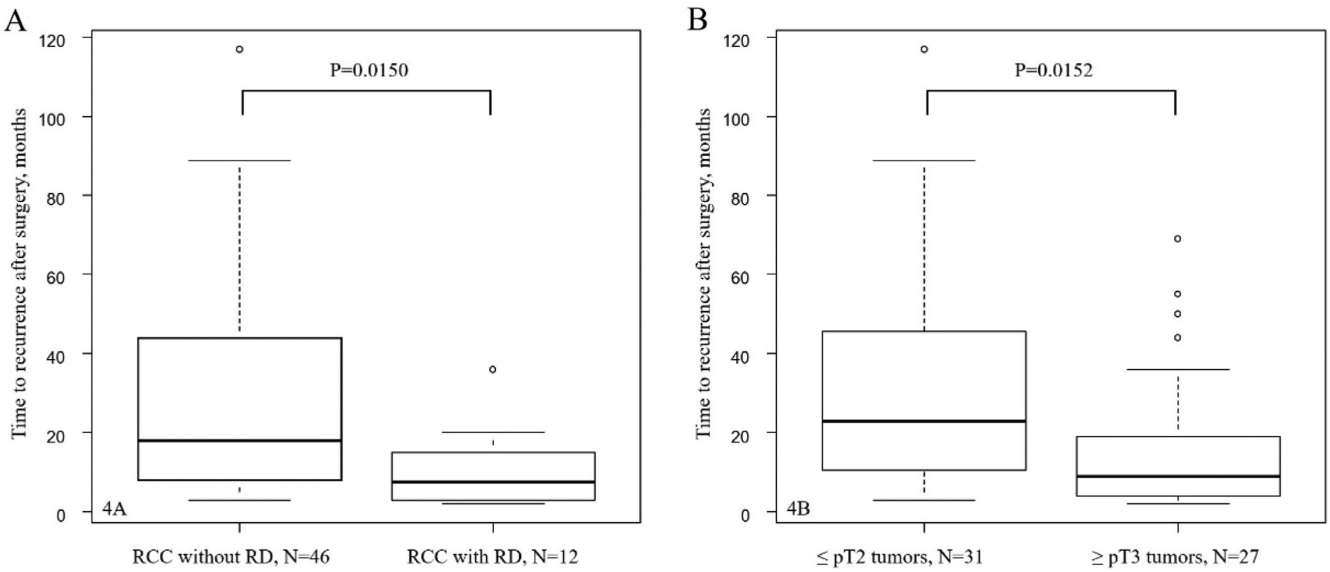

Fig. 4. Comparison of mean time to recurrence after surgery in 58 patients with postoperative recurrence. Data are represented in box-and-whisker plots showing median, minimum, lower quartile, upper quartile, and maximum. There are significant differences A, between renal cell carcinoma with and without rhabdoid differentiation ($P = 0.0150$), and B, between ≤pT2 tumors and ≥pT3 tumors ($P = 0.0152$).

5. Conclusions

The impact of the presence of RD in RCC on the postoperative recurrence of patients with N0M0 RCC was demonstrated using a propensity score-matched cohort and entire cohort of 604 patients. The result of subgroup analysis showed that the presence of RD in RCC was more important in predicting poor RFS and CSS in the early pT category subgroup than in the advanced pT category subgroup. The shorter TTR in patients with RD indicates the need for intensive follow-up during the postoperative period.

Conflicts of interest

The authors declare no conflict of interest.

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