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Nephrometry score correlated with tumor proliferative activity inT1 clear cell renal cell carcinoma

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Abstract

Objective: To evaluate the association between the RENAL nephrometry score (RNS) and tumor proliferative activity assessed by immunohistochemistry in patients with localized renal cell carcinoma.

Methods: The current study included 145 pathological T1 (pT1) clear cell renal cell carcinomas (ccRCC). Tumor proliferative activity was assessed with the Ki67 index and microvessel density (MVD). RNS was retrospectively assessed in the present study. We divided patients into 3 groups according to RNS (RNS 4−6: low-complexity, 7−9: moderate complexity, and 10−12: high-complexity tumors) and compared the Ki67 index as well as MVD among the 3 groups. The association between the Ki67 index/MVD and each component (R, E, N, A, L, h) was also evaluated.

Results: There were 56 low, 84 moderate, and 5 high-complexity tumors. The median Ki67 index of all tumors was 5.34% (interquartile range: 3.28−8.57). The median Ki67 index of low, moderate, and high-complexity tumors was 3.97%, 6.39%, and 11.27%, respectively, with a significant difference among the 3 groups (Kruskal−Wallis test, $P = 0.0004$). On the other hand, the median MVD of low, moderate, and high-complexity tumors was 14.11%, 14.42%, and 21.22%, respectively, and there were no significant differences among the 3 groups. In terms of each RNS component, there were significant differences in the Ki67 index among the 3 groups in N ($P = 0.0101$) and L ($P = 0.0280$) components, respectively.

Conclusions: The revealed association between RNS and the Ki67 index in pT1 clear cell renal cell carcinomas further supports the previous findings that the anatomy of renal cell carcinoma is associated with the malignant potential of localized clear cell renal cell carcinoma, which may provide additional information for treatment decision. © 2019 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license. (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Keywords: Ki67 index; Microvessel density; Kidney; Neoplasms; RENAL nephrometry score

1. Introduction

Based on widespread screening and advances in imaging modalities, the rate of detecting small renal tumors has steadily increased [1,2]. Of those small renal tumors, clear cell renal cell carcinoma (ccRCC) is the most frequent form of sporadic RCC [3]. Nephron-sparing approaches such as partial nephrectomy, cryotherapy, or thermal ablation are now available for the treatment of small renal tumors [4]. In addition, thanks to accumulated information on the relatively indolent natural course of small renal tumors, active surveillance is another option [5,6], and predictors of the tumor growth rate could be beneficial for treatment decisions, especially when patients already have competing health risks. Our group previously reported that the RENAL Nephrometry Score (RNS), which is now widely utilized to assess anatomical features of renal tumors, was associated with the annual tumor growth rate on linear regression analysis in 47 renal tumor patients with at least 12-month follow-up [7]. Mehrazin et al. also

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reported a similar observation on analyzing 401 small renal masses, whereby the average tumor linear growth rate increased by 0.037 cm/y for each 1-point increase in RNS [8]. Furthermore, other researchers reported that a high RNS was associated with unfavorable pathology in RCC patients [9]. These observations strongly suggest that anatomic features of renal cell carcinomas are associated with tumor proliferative ability and the malignant potential.

Ki67 is a proliferation marker that is expressed during the cell cycles of G1, S, G2, and M stages. Several studies reported that Ki67 expression is associated with a poor prognosis in patients with several types of cancer including renal cell carcinoma [10,11]. Microvessel density (MVD), considered to be a surrogate marker of a tumor's angiogenic potential, has also been associated with a poor prognosis in patients with a number of malignancies including renal cell carcinoma [12]. In the present study, in order to gain further insights into the association between the anatomy of small ccRCC and tumor proliferative activities, we assessed the Ki67 index and MVD by immunohistochemistry in pT1 renal cell carcinoma patients, and evaluated the association between these results and RNS.

2. Materials and Methods

2.1. Study population

This study was approved by the Institutional Review Board of Hokkaido University Hospital. Between January 2002 and December 2014, open or laparoscopic partial nephrectomy for small renal tumors was performed in 253 cases (246 patients) at Hokkaido University Hospital. Excluding those with recurrent ($n = 10$) or multiple tumors ($n = 28$), 215 were treated for single primary renal tumors. Among these cases, 152 patients were pathologically diagnosed with pT1 ccRCC. Excluding cases with a missing preoperative image ($n = 6$), or insufficient pathological information ($n = 1$), 145 patients were included in the present study. This inclusion flow is summarized in Supplementary Figure 1. Patients' characteristics including age, sex, tumor size, tumor location, and pathological outcomes were retrospectively collected from the medical charts. The histological grade was defined by the Japanese pathological criteria. It is based on nuclear morphology. It is divided into grades 1, 2, and 3 (Grade 1, tumors have smaller nuclei than renal tubular epithelial cells; Grade 2, tumors have the same sized nuclei as renal tubular epithelial cells; and Grade 3, tumors have larger nuclei than renal tubular epithelial cells, as well as more irregular and pleomorphic nuclei). Using preoperative computed tomography imaging, tumors were classified by RNS as well as its individual components [13]. RNS is based on 5 anatomical parameters: (R)adius (largest diameter), (E)xophytic/endophytic natures of the tumor, (N)earness of the deepest part of the tumor to the collecting system or sinus, (A)nterior (a)/posterior (p) descriptor, and the (L)ocation relative to the polar line. All components other than (A) are recorded on a 1, 2, or 3-point scale. The (A) describes the mass location to the coronal plane of the kidney. The suffix "x" is assigned if anterior or posterior tumor designation is not possible. An additional suffix "h" is utilized to designate a hilar location of the tumor (abutting the main renal artery or vein) [13]. RNS was determined by consensus between 2 senior urologists. For subsequent analyses, RNS of 4 to 6, 7 to 10, and 10 or greater were classified as low, intermediate, and high complexity, respectively, and we compared the Ki67 index as well as MVD among the 3 groups, and between the low- and moderate/high-complexity groups. The association between each component of RNS and the Ki67 index or MVD was also evaluated.

2.2. Immunohistochemistry

Immunohistochemical staining was performed at Morphotechnology Company Limited (Sapporo, Japan). Anti-Ki67 monoclonal antibody (clone Ki67, Dako M7240, 1:150) was used for Ki67 detection. Anti-CD34 monoclonal antibody (clone QBEnd 10, Dako F7166, 1:300) was used for blood vessel detection. Representative parts of cancer tissues were stained, and sample images were acquired using NanoZoomer (Hamamatsu Photonics, Japan).

2.3. Ki67 index analysis

The 5 fields with the highest density of Ki67-positive nuclei were selected. The Ki67-positive or -negative nuclei number at low magnification (×100) was determined using Image J software (National Institutes of Health, Bethesda, MD, USA) and Gunma-LI, Version 017 (Japan Brain Tumor Reference Center, Gunma, Japan) [14]. The Ki67 index was calculated as the number of positively Ki67-stained nuclei expressed as a ratio of the total nuclei using the average of 5 fields.

2.4. Micro-vessel density analysis

The 5 most vascularized fields within each CD34-stained section were selected. MVD was quantified at low magnification (×100) using Image J software. MVD was determined as the CD34-stained area as a percentage of the total area using the average of 5 fields [15].

2.5. Statistical analysis

Outlier box plots represent the median (center line) and 25th and 75th percentiles (box), and the ends of the whiskers are the outermost data points from their respective quartiles that fall within the distance computed as 1.5 times the interquartile range (IQR). The Kruskal−Wallis test was performed for multiple comparisons, followed by the Wilcoxon test for paired comparisons. JMP version 13 (SAS

Institute, Tokyo, Japan) was used for all calculations, and $P < 0.05$ was considered significant.

3. Results

The clinical and pathological features of the 145 ccRCCs are shown in Table 1. The median patient age was 63 years (range: 30−85 years). The median tumor size at surgery was 2.4 cm (range: 1.0−6.3). The median RNS based on the initial image was 7 (range: 4−10). These included 56 low (RNS 4−6), 84 moderate (RNS 7−9), and 5 high-complexity (RNS 10−12) tumors. Representative images of Ki67 and CD34 staining in ccRCCs are shown in Fig. 1.

Fig. 2 and Table 2 show the association between RNS and the Ki67 index. The median Ki67 index of all tumors was 5.34% (IQR: 3.28−8.57), and those of low, moderate, and high-complexity tumors were 3.97% (IQR: 2.34−6.43), 6.39% (IQR: 4.11−8.98), and 11.27% (IQR: 5.88−17.63), respectively. There were significant differences in the Ki67 index among the 3 groups (Fig. 2A), as well as between the low and moderate/high groups (Fig. 2B). The Ki67 index of moderate or high-complexity tumors was significantly higher than that of low-complexity tumors (Fig. 2A). In terms of the association between each RNS component and the Ki67 index, N ($P = 0.0101$) and L ($P = 0.0280$) components were significantly associated with the Ki67 index (Table 2, and Supplementary Figure 2).

Fig. 3 and Table 3 show the association between RNS and MVD. The median MVD of all tumors was 14.51% (IQR: 10.82−20.90), and those of low, moderate, and high-complexity tumors were 14.11% (IQR: 10.20−20.66), 14.42% (IQR: 10.82−20.03), and 21.22% (IQR: 16.21−25.24), respectively. There was no significant difference in MVD among the 3 groups of RNS, on comparing each component (Table 3, Fig. 3A, and Supplementary Figure 3). Similarly, there was no significant difference in MVD between the low and moderate/high groups (Fig. 3B).

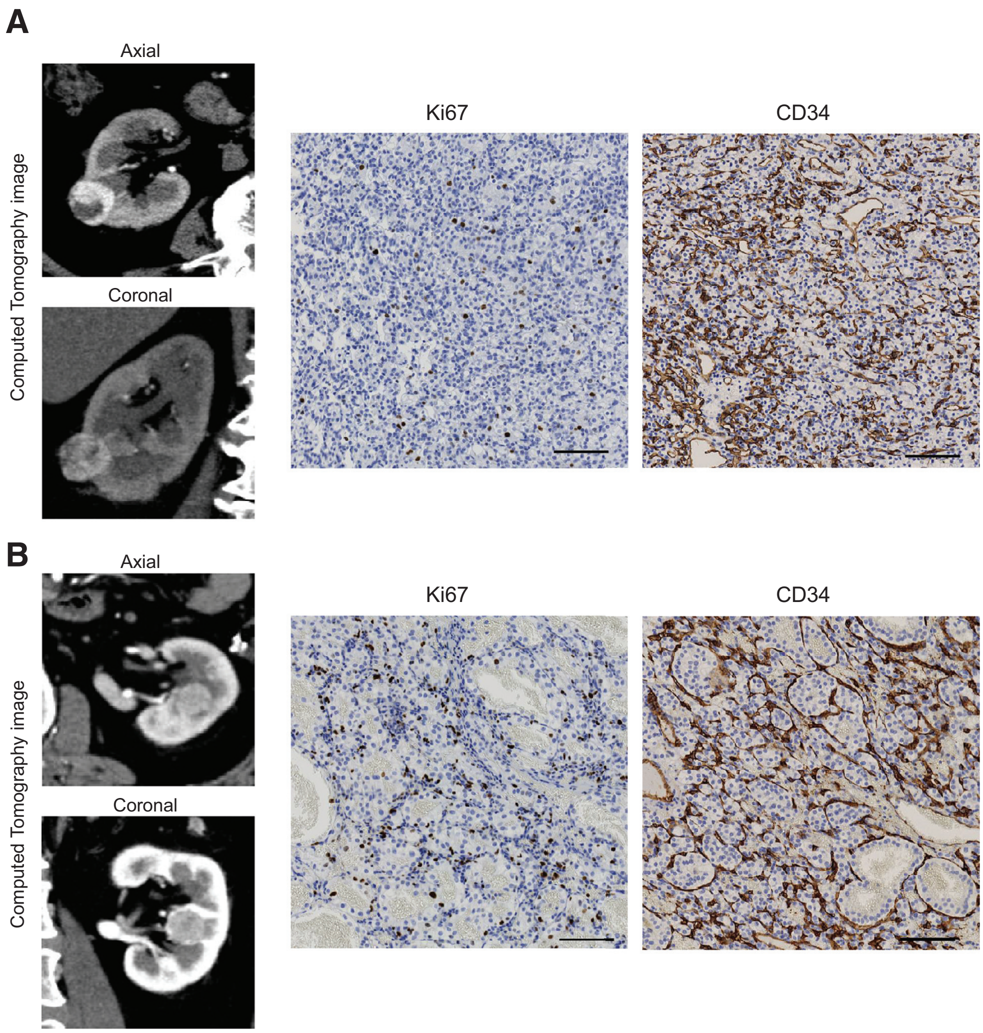
4. Discussion

Based on the increased incidental detection of small renal mass, especially in the elderly or patients with pre-existing comorbidities, it is becoming more important to predict malignancy or its aggressiveness before treatment decisions. Modern renal biopsy series have reported a high accuracy of over 90% for determining tumor malignancy [16−18]. However, the accuracy for tumor grading is still limited (around 40%−60% accuracies reported) [18−20] and the underuse of renal biopsy has also been pointed out in actual clinical practice [21], which means that radiological characteristics play a major role in determining the management. Recently, Kutikov and Uzzo developed the RNS system to standardize assessment of the anatomical characteristics of renal masses [13], and subsequently reported that RNS was correlated with both the tumor grade and histology, such that large interpolar and hilar tumors were more likely to represent high-grade cancers [9]. Their group also reported the association between RNS and the linear growth rate in 401 masses with a surveillance duration of at least 6 months [8]. In the present study, using an immunohistochemical method, we supported previous

Table 1
Tumor characteristics ($n = 145$)

Variables	All tumors ($n = 145$)	Tumor complexity: Low ($n = 56$)	Tumor complexity: Moderate/High ($n = 89$)
Age at surgery, year, median (range)	63 (30−85)	66 (33−85)	62 (30−82)
Sex, no. (%)			
Male	103 (71.0)	40 (71.4)	63 (70.8)
Female	42 (29.0)	16 (28.6)	26 (29.2)
Tumor size, cm, median (range)	2.4 (1.0−6.3)	2.3 (1.2−4.1)	2.6 (1.0−6.3)
cT1a: cT1b	133:12	45:1	78:11
RENAL nephrometry score, median (range)	7 (4−10)	5 (4−6)	8 (7−10)
R, median (range)	1 (1−2)	1 (1−2)	1 (1−2)
E, median (range)	2 (1−3)	1 (1−3)	2 (1−3)
N, median (range)	2 (1−3)	2 (1−3)	3 (1−3)
A, no. (%)			
A	58 (40.0)	23 (41.1)	35 (39.4)
P	42 (29.0)	15 (26.9)	27 (30.3)
x	45 (31.0)	18 (32.0)	27 (30.3)
L, median (range)	2 (1−3)	1 (1−3)	3 (1−3)
Grade*, no. (%)			
G1	12 (8.3)	8 (14.3)	4 (4.5)
G2	113 (78.5)	44 (78.6)	69 (77.5)
G3	20 (13.8)	4 (7.1)	16 (18.0)
pT1a: pT1b	136:9	56:0	80:9

* Histological grade was defined by Japanese pathological criteria



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Case	Age (years)	Sex	Tumor size (cm)	RENAL nephrometry score by component	Ki67 index (%)	MVD (%)	pT stage	Grade
A	69	Female	2.4	1+1+1+x+2=5x	3.57	13.79	1a	G2>G1
B	63	Male	1.8	1+3+3+x+3=10x	19.58	12.10	1a	G2

Fig. 1. Representative cases with low-complexity (A) or high-complexity (B) tumor.
(A), (B) Axial and Sagittal Computed Tomography Image and immunostaining of Ki67 and CD34 in low-complexity (A) or high-complexity (B) tumor (magnification ×100. Scale bar: 100 μm). (C) The clinical features, Ki67 index, and MVD of 2 cases are shown.

observations including ours that RNS was associated with the annual tumor growth rate of small renal tumors. As shown in Fig. 2A and Table 2, there were significant differences in the Ki67 index among low, moderate, and high-complexity groups (median Ki67 index: 3.97% vs. 6.39% vs. 11.27%, respectively, Kruskal−Wallis test, P = 0.0004). When combining the moderate and high-complexity groups together, similarly, we observed a significant difference in the Ki67 index between the low and moderate/high-complexity groups (Fig. 2B, P = 0.0003). We consider that our observations further support the relationship between anatomical features and biological characteristics in small renal cell carcinoma. Out of the 145 cases, there were 21 overlapping with our previous study [7], which meant that 21 had data on annual tumor growth rates before surgery. In these 21 cases, the Ki67 index was significantly correlated with the annual growth rate (Spearman correlation = 0.6074, P = 0.0035, data not shown).

Regarding the clinicopathological role of Ki67 expression in RCC, Gayed et al. previously reported that, out of 401 patients, high expression of Ki67 (≥10% tissue positivity) was noted in 6.5% and associated with adverse

Table 2
Association between the RENAL nephrometry score and Ki67 index

	Ki67 index (%) Median (IQR)	*P* value (Kruskal−Wallis test)
All tumors (*n* = 145)	5.34 (3.28−8.57)	
Complexity		0.0004
Low (RNS: 4−6, *n* = 56)	3.97 (2.34−6.43)	
Moderate (RNS: 7−9, *n* = 84)	6.39 (4.11−8.98)	
High (RNS: 10−12, *n* = 5)	11.27 (5.88−17.63)	
R score		0.1079
1 (*n* = 133)	5.20 (3.19−8.47)	
2 (*n* = 12)	7.46 (4.68−13.25)	
E score		0.3215
1 (*n* = 43)	4.77 (2.35−7.68)	
2 (*n* = 89)	5.73 (3.62−8.85)	
3 (*n* = 13)	5.42 (3.59−7.87)	
N score		0.0101
1 (*n* = 52)	4.44 (2.27−6.76)	
2 (*n* = 29)	5.50 (2.39−8.66)	
3 (*n* = 64)	6.42 (4.12−8.91)	
A score		0.7384
a (*n* = 58)	5.43 (3.35−8.34)	
p (*n* = 42)	5.97 (4.12−8.05)	
x (*n* = 45)	4.68 (2.33−10.22)	
L score		0.0283
1 (*n* = 58)	4.65 (2.36−6.82)	
2 (*n* = 34)	6.91 (3.31−9.89)	
3 (*n* = 53)	5.85 (4.05−9.35)	
Hilar location		0.0751
−(*n* = 133)	5.20 (3.19−8.36)	
+(*n* = 12)	8.16 (5.06−13.47)	

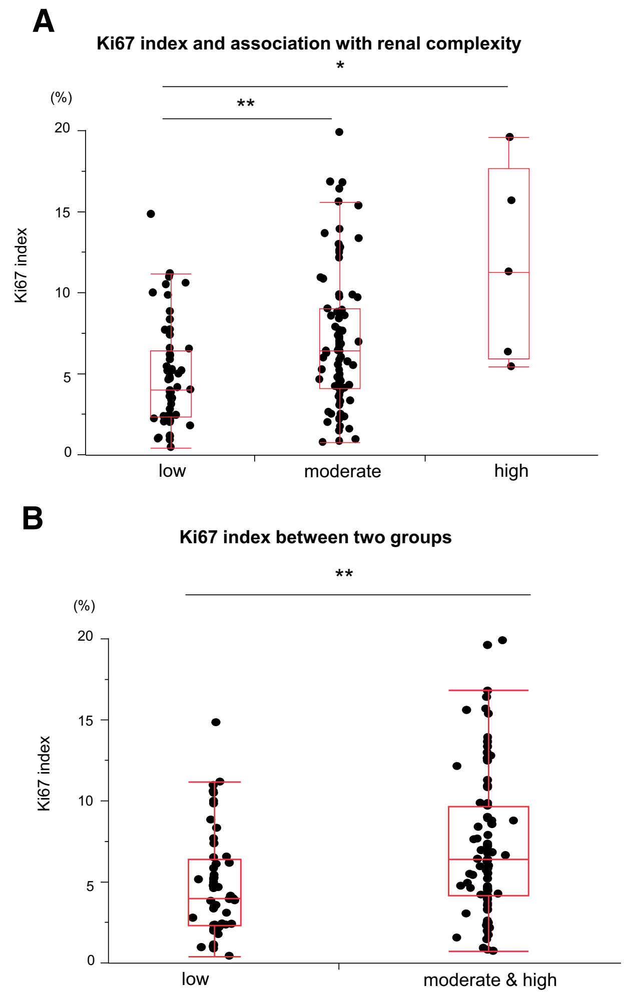

Fig. 2. Ki67 index and association with renal complexity.
(A) Dot plot showing the Ki67 index in low, moderate, and high-complexity tumors. Statistical significance was determined with the Kruskal−Wallis test followed by the Wilcoxon test. * $P < 0.05$, ** $P < 0.001$. (B) Dot plot showing the Ki67 index in low and moderate/high-complexity tumors. Statistical significance was determined with the Wilcoxon test. ** $P \leq 0.001$

pathological features (T stage, Grade, Tumor size ≥5 cm, sarcomatoid differentiation, tumor necrosis, and lymphovascular invasion) [10]. We also observed significant differences in the Ki67 index among grade 1, 2, and 3 tumors (median Ki67 index: 2.86% vs. 5.43% vs. 8.33%, respectively, Kruskal−Wallis test, $P = 0.0009$, data not shown).

Regarding each component of RNS, N and L components were associated with an increased Ki67 index. Mehrazin et al. also reported that R, E, and N components were associated with an increased linear growth rate of renal tumors, and, moreover, the N component was strongly associated with this ($P < 0.0001$) [8]. In addition, Correa et al. observed that, in 334 renal tumors less than 4 cm, the N component, defined as less than 4 mm from the collecting system or renal sinus fat, was the only anatomical feature associated with a diagnosis of cancer (odds ratio, 3.58, $P = 0.04$) as well as high-grade histology (odds ratio, 2.81, $P = 0.003$) [22]. Although the mechanism explaining the relationship between a central tumor location and marked probability of high-grade disease has not been clarified yet, Correa et al. postulated that, due to increased extracellular tonicity and decreased oxygen tension in the microenvironment of the inner renal medulla, normal renal tubule cells induce cell-protecting pathways, such as the hypoxia-inducible factor pathway, and these pathways are also utilized by cancer cells to promote growth and survival.

In the present study, considering the potential relationship between angiogenesis and tumor growth, MVD was also evaluated using anti-CD34 monoclonal antibody, which showed no significant difference in MVD among the 3 groups of RNS, between the low- and moderate/high-complexity groups, or either in terms of each component. In terms of the survival impact of MVD in RCC, there have been conflicting observations. Several researchers reported that a higher blood vessel density in RCC indicates a better prognosis, whereas some researchers reported an inverse relationship [23−26]. There are several endothelial markers such as CD31 or CD105. Those endothelial markers are heterogeneous and are known to reveal different characteristics of tumor blood vessels. For example, CD34 is known

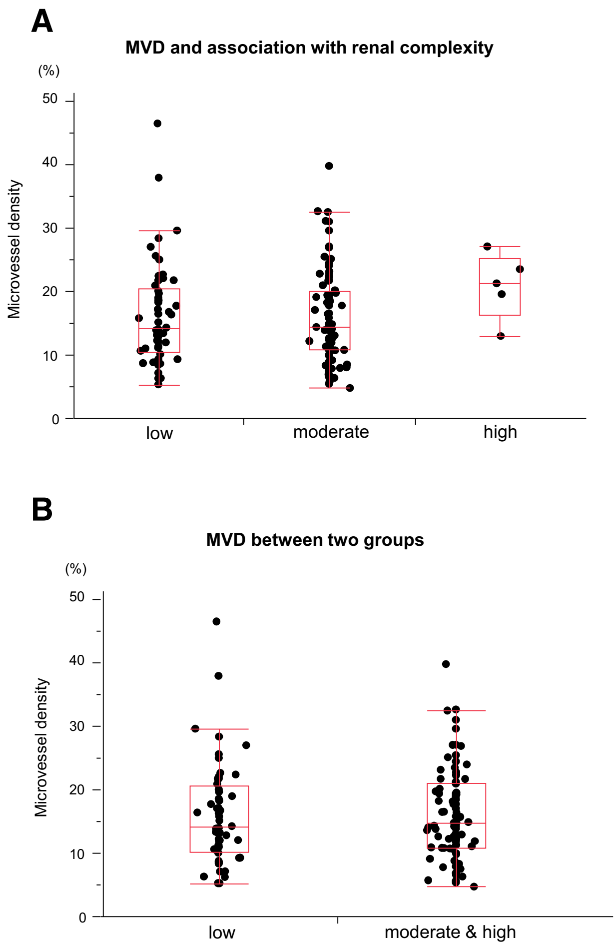

Fig. 3. MVD and association with renal complexity.
(A) Dot plot showing MVD in low, moderate, and high-complexity tumors. Statistical significance was determined with the Kruskal−Wallis test. There was no significant difference between the groups. (B) Dot plot showing MVD in low and moderate/high-complexity tumors. Statistical significance was determined with the Wilcoxon test. There was no significant difference between the groups.

Table 3
Association between RENAL nephrometry score and MVD.

	MVD (%) Median (IQR)	*P* value (Kruskal−Wallis test)
All tumors ($n = 145$)	14.51 (10.82−20.90)	
Complexity		0.1924
Low (RNS: 4−6, $n = 56$)	14.11 (10.20−20.66)	
Moderate (RNS: 7−9, $n = 84$)	14.42 (10.82−20.03)	
High (RNS: 10−12, $n = 5$)	21.22 (16.21−25.24)	
R score		0.8746
1 ($n = 133$)	14.33 (10.86−20.90)	
2 ($n = 12$)	19.23 (7.26−20.83)	
E score		0.8023
1 ($n = 43$)	14.24 (10.06−20.01)	
2 ($n = 89$)	14.51 (10.86−21.07)	
3 ($n = 13$)	16.39 (10.92−23.69)	
N score		0.0896
1 ($n = 52$)	16.01 (11.28−20.58)	
2 ($n = 29$)	11.83 (8.62−17.53)	
3 ($n = 64$)	15.30 (11.26−22.34)	
A score		0.4712
a ($n = 58$)	14.93 (10.88−21.00)	
p ($n = 42$)	13.30 (9.13−19.82)	
x ($n = 45$)	15.75 (11.48−21.58)	
L score		0.5250
1 ($n = 58$)	14.95 (10.47−21.68)	
2 ($n = 34$)	12.63 (8.39−21.86)	
3 ($n = 53$)	14.86 (11.17−20.29)	
Hilar location		0.4052
−($n = 133$)	14.24 (10.86−20.50)	
+($n = 12$)	17.72 (10.67−25.58)	

to be expressed in differentiated endothelial cells, whereas CD31 is expressed in both differentiated and undifferentiated endothelial cells [27]. It has been reported that CD31-positive and CD34-negative blood vessels were determined as undifferentiated vessels and the vessel density was associated with a poor prognosis in ccRCC patients [28]. Further studies may be required to verify the correlation between immature blood vessel formation and RNS using other endothelial antibodies.

In terms of survival, which was not our main aim, 7 patients developed disease recurrence after surgery. There was no significant difference in recurrence rate between the low and moderate/high groups (5-year recurrence-free survival: low: 97.1%, moderate/high: 94.5%, log-rank test, $P = 0.4724$).

The present study had several limitations. First, the sample size was small, and the present cohort contained a few high-complexity tumors ($n = 5$). Also, this cohort contained a few tumors with a radius score of 2 ($n = 12$) and a few with a hilar location ($n = 12$). We are planning to expand the high-complexity cohort in a multi-institutional setting. Second, no central pathological review was performed. Third, as described above, different endothelial markers might generate different results in terms of the association between MVD and RNS. However, we consider that several interesting observations were made in this study. As the next step, we are planning a new study to evaluate whether the Ki67 index could be effectively evaluated by needle biopsy, and whether the combined use of the Ki67 index and RNS score could be used to more accurately to predict the tumor growth rate.

5. Conclusions

RNS was associated with the Ki-67 index in pT1 ccRCC patients, but was not associated with MVD. Our observations further support the previous findings that the anatomy of renal cell carcinoma is associated with the malignant potential in localized ccRCC, which may give us additional information for treatment decision.

Conflict of interest

None declared.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.02.005.

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