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Original Contributions

Microscopic and nuclear morphometric findings of chromophobe renal cell carcinoma, renal oncocytoma, and tumor with overlapping histology ☆

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Abstract We compared the microscopic and nuclear morphometric characteristics of classical chromophobe renal cell carcinoma (C-ChRC) and renal oncocytoma (RO) and applied meaningful characteristics to differentiate eosinophilic chromophobe renal cell carcinoma (E-ChRC) from RO that has overlapping histology (RO-OH) with E-ChRC to know the usefulness of nuclear morphometry. Microscopic and morphometric characteristics were evaluated in 24 C-ChRCs, 6 E-ChRCs, 5 RO-OHs, and 25 classical ROs (C-ROs). The microscopic findings favoring C-ChRC were rasinoid nuclei, perinuclear halo, and distinct cytoplasmic membrane. Characteristic for C-RO was either stromal edema or hyalinization. The morphometric values of nearest nuclear distance, shortest nuclear diameter, and nuclear diameter ratio were significantly different between C-ChRC and C-RO. However, it was impossible to distinguish E-ChRC from RO-OH by histology and nuclear morphometry. The results of our study show that nuclear morphometry and histomorphology can distinguish between C-ChRC and C-RO but not between E-ChRC and RO-OH.
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1. Introduction

The renal cell carcinoma is the most common type of kidney cancer in the adult, and its incidence has been increasing in the last few decades [1]. The common histologic types of renal cell carcinoma are clear cell carcinoma, papillary carcinoma, chromophobe renal cell carcinoma (ChRC), and collecting duct carcinoma. In most cases, it is not difficult to make a correct diagnosis. However, diagnostic challenges sometimes occur between ChRC and renal oncocytoma (RO) or clear cell and papillary renal cell carcinomas, respectively [2].

The ChRC reveals morphological characteristics, which are distinct cell membrane, perinuclear clearing, and raisinoid nucleus. It constitutes 5% to 8% of renal cell carcinomas [3]. Thoenes et al [4] first described ChRC in 1985, and they also described the eosinophilic ChRC (E-ChRC) [5]. Renal oncocytoma is a benign renal epithelial tumor that is characterized by uniform nuclear size and shape, densely eosinophilic cytoplasm, and stromal hyalinization. We designated the tumors that reveal typical morphology of either ChRC and RO as classical ChRC (C-ChRC) and classical RO (C-RO), respectively. However, a few of ROs reveal irregular nuclear size and coarsely clumped chromatin, which overlaps the features of E-ChRC. We designated them as RO with overlapping histology (RO-OH).

☆ Conflict of interest statement: We declare that we have no conflict of interest.

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The ChRC and RO are considered as a same spectrum of diseases. Both of them are originated from intercalated cell of distal tubule and reveal similar genetic changes. Because ChRC has worse clinical outcome, it is important to distinguish between them. In most cases, it is not difficult to differentiate them by morphological features. However, it is sometimes very difficult by histomorphology. Several studies using immunohistochemical markers, histochemical stain, and electron microscopic examination have been introduced. Cytokeratin (CK) 7 [6], parvalbumin [6], S100A1 [7,8], MOC31 [9], C-kit [10] and anticaveolin 1 [9] as well as histochemical stain such as Hale colloidal iron stain [11] are known to be useful. Recently, we reported that a panel of immunohistochemical markers (CK7, S100A1, and claudin 8) was useful to differentiate ChRC from RO [12]. However, ancillary tests of immunohistochemistry or histochemistry have limitations in sensitivity, specificity, and reproducibility in some extent.

The morphometric analysis has been used to determine the grade and predict the prognosis of renal diseases [13,14]. It also has been used to differentiate benign from malignant lesions [15]. Morphometric study is thought to be objective and a reproducible method to examine the microscopic features [16]. We expected that morphometric evaluation would reveal the overlooked histomorphological characteristics of lesions. We introduced nuclear morphometry to distinction of categories of overlapping histology.

In this study, we compared microscopic and nuclear morphometric features of C-ChRCs and C-ROs and applied the discriminating features to differentiate E-ChRCs from RO-OHs.

2. Materials and methods

2.1. Case selection

Sixty cases diagnosed as either ChRC or RO have been retrieved from the files of the Departments of Pathology of Seoul National University Hospital (2004-2007), Chonnam National University Hospital (2000-2007), and Asan Medical Center (2004-2007).

2.2. Macroscopic and microscopic examinations

All of the specimens were fixed in 10% neutral-buffered formalin and embedded in paraffin using standard pathology protocols. Sections were cut 3-μm thick and stained with hematoxylin and eosin (H-E). The macroscopic description and H-E slides of all cases were reviewed by 3 pathologists (SSK, CC, and YDC). The diagnoses of ChRC and RO were made from H-E–stained slides according to the World Health Classification 2004 Classification of Tumours of the Urinary System and Male Genital Organ [3]. They were classified as 24 C-ChRCs, 25 C-ROs, 6 E-ChRCs, and 5 RO-OHs by immunohistochemical stains and electron microscopic examination, as described previously [12].

Microscopic findings of the nuclear, cytoplasmic, and stromal features were assessed. All of the features were classified as 2-tier grade system. Thus, nuclear pleomorphism was graded as mild to moderate and marked. Nuclear membrane irregularity was classified as smooth to intermediate and raisinoid. Chromatin pattern was graded as uniform to finely clumped and coarsely clumped. Cytoplasmic texture was graded as clear to slightly eosinophilic and densely eosinophilic. Presence of perinuclear halo and distinct cytoplasmic membrane was defined when they could be recognized in more than 5% of the tumor cells at magnification ×100 (Fig. 1).

2.3. Morphometry

For morphometric analysis, a random selection of 10 microscopic high-power field (×400) images of hematoxylin-stained slides was made. Areas of necrosis, degeneration, hemorrhage, or cystic change were avoided. The microscopic images of the prepared sections were obtained with a microscope (Eclipse 90i; Nikon, Tokyo, Japan) equipped with a high-resolution camera (Digital Camera DXM1200C; Nikon). All digital images (24-bit color and 4116 × 3072 pixel resolution) were saved in Joint Photographic Experts Group file format. Soft Imaging System GmbH equipment and analySIS software (Master, Munster, Germany) were used for image analysis. Nuclear morphometry was performed on representative images by a pathologist blinded to the histologic diagnosis. For epithelial tumor cells, only the nuclei with sharp borders were measured. More than 200 nuclei (mean count, 419) were measured in each case.

In each case, the longest nuclear diameter (LD), the shortest nuclear diameter (SD), and the nearest nuclear distance (NND) were measured, and their mean value, SD, and coefficient of variation were calculated. The LD and SD were used as geometric parameters, representing the real length along the major and minor axes of the nucleus. The *NND* was defined as the distance between the center of the nucleus and the nearest nucleus.

The cross-sectional nuclear area (AR) was calculated in square micrometer, as follows:

$$\mathrm{AR} = \frac{1}{4}\pi \times LD \times SD.$$

The nuclear diameter ratio (DR), that is, the degree of nuclear ellipticity, was calculated as follows:

$$DR = LD/SD.$$

2.4. Statistical analysis

The results were analyzed using the Kruskal-Wallis test to describe the statistical differences between the disease groups. Post hoc comparisons between pairs were made by the Mann-Whitney *U* test, with the $P \leq .0125$ as statistically significant. Multivariate logistic regression analysis was

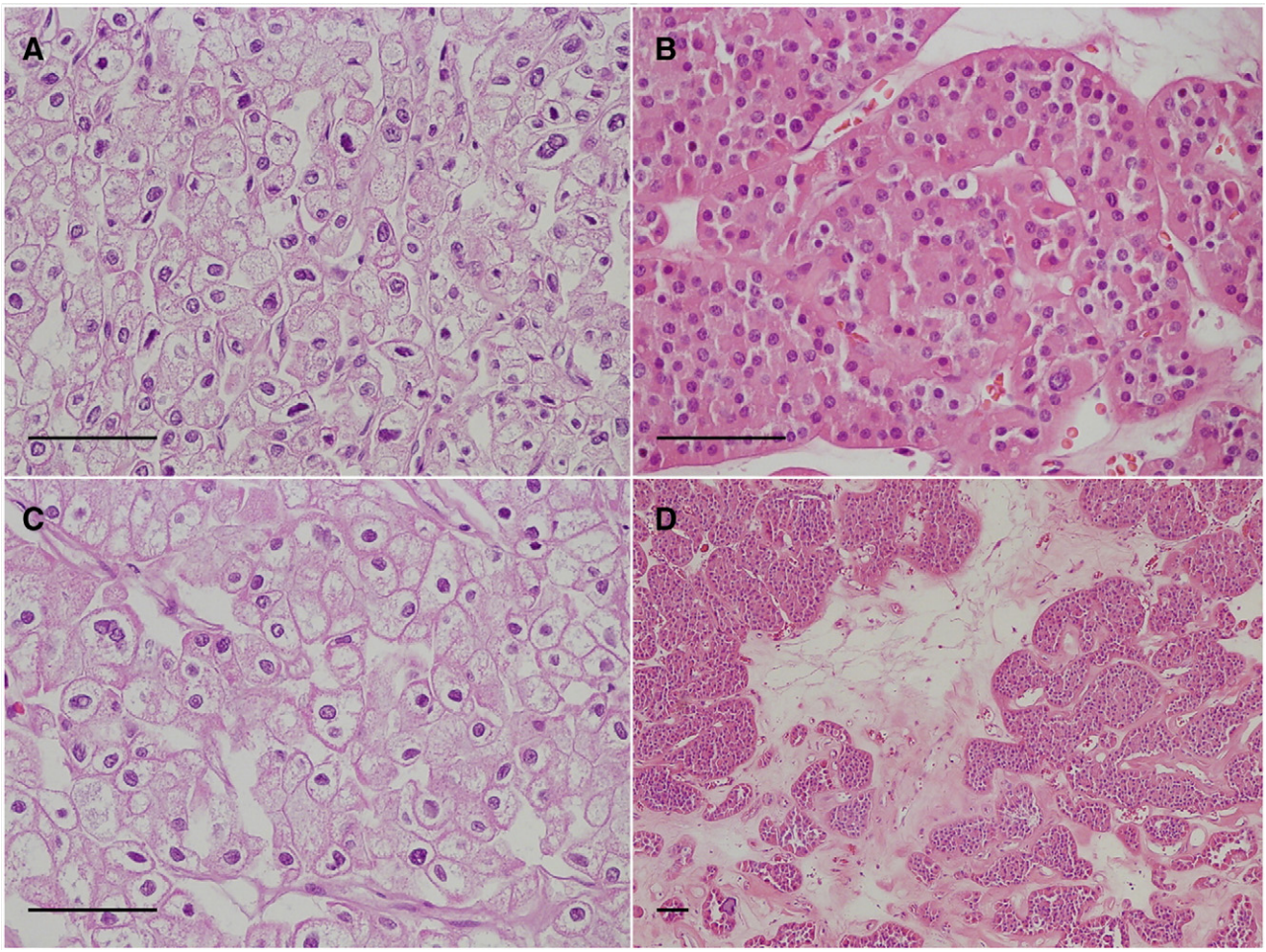

Fig. 1. Morphological findings of C-ChRC and C-RO. A, A case of C-ChRC with marked nuclear pleomorphism, rasinoid nuclear membrane, perinuclear halo, and prominent cell border is presented. B, A case of C-RO shows smooth nuclear membrane, densely eosinophilic cytoplasm, and stromal edema. C, A case of C-ChRC reveals moderate nuclear pleomorphism and coarsely clumped chromatin pattern. D, A case of C-RO displays stromal edema and hyalinization. The scale bar represents 100μm.

used to predict the significant nuclear morphometric variables for discriminating C-ChRCs from C-ROs.

3. Results

3.1. Clinical and macroscopic findings

The clinical and macroscopic findings are summarized in Table 1. Most patients (51/59, or 86.4%) visited the hospital for evaluation of incidentally detected renal mass, whereas 8 (13.6%) of 59 were symptomatic. Both C-ChRC and C-RO showed slight female predominance. The diameter of the C-ChRCs (4.7 ± 2.7 cm, mean ± SD) was larger than that of C-RO (3.5 ± 2.2 cm). Scar formation was more commonly found in ROs (12/25, or 48%) than in ChRCs (2/24, or 8%) ($P < .01$). Hemorrhage was variably observed in C-ChRC (5/24, or 20.8%) and C-RO (8/25, or 32%). However, there was no statistical difference in patient's age, tumor diameter, and macroscopic hemorrhage between C-ChRCs and C-ROs.

3.2. Microscopic findings

The microscopic findings are summarized in Table 2. The features favoring C-ChRC rather than C-RO were perinuclear halo, prominent cell border, clear to slightly

Table 1
Clinical and macroscopic findings of renal tumors

Parameters	C-ChRC	E-ChRC	RO-OH	C-RO
Total (n)	24	6	5	25
Female (n)	14	2	2	14
Male (n)	10	4	3	11
Age (y)	55.2 ± 14.5	67.0 ± 12.54	55.8 ± 23.87	54.8 ± 8.5
Gross finding				
Diameter (cm)	4.7 ± 2.7	3.86 ± 2.43	4.06 ± 1.48	3.5 ± 2.2
Scar (n)	2	2	1	12
Hemorrhage (n)	5	2	1	8
Chief complaint				
None (n)	19	5	5	23
Flank pain (n)	4	1	0	1
Hematuria (n)	1	0	0	1

Table 2
Microscopic findings of renal tumors

	C-ChRC (%) (n = 24)		E-ChRC (%) (n = 6)		RO-OH (%) (n = 5)		C-RO (%) (n = 25)	
Nuclear pleomorphism								
Mild to moderate	7	(29.2)	6	(100.0)	2	(40.0)	24	(96.0)
Marked	17	(70.8)	0	(0.0)	3	(60.0)	1	(4.0)
Nuclear membrane irregularity								
Smooth to intermediate	6	(25.0)	6	(100.0)	2	(40.0)	25	(100.0)
Raisinoid	18	(75.0)	0	(0.0)	3	(60.0)	0	(0.0)
Chromatin pattern								
Uniform to finely clumped	8	(33.3)	4	(66.7)	1	(20.0)	24	(96.0)
Coarsely clumped	16	(66.7)	2	(33.3)	4	(80.0)	1	(4.0)
Cytoplasm								
Clear to slightly eosinophilic	21	(87.5)	1	(16.7)	0	(0.0)	0	(0.0)
Densely eosinophilic	3	(12.5)	5	(83.3)	5	(100.0)	25	(100.0)
Perinuclear halo								
Yes	24	(100.0)	0	(0.0)	1	(20.0)	0	(0.0)
No	0	(0.0)	6	(100.0)	4	(80.0)	25	(100.0)
Prominent cell border								
Yes	23	(95.8)	0	(0.0)	0	(0.0)	0	(0.0)
No	1	(4.2)	6	(100.0)	5	(100.0)	25	(100.0)
Stromal edema or hyalinization								
Yes	2	(8.3)	1	(16.7)	3	(60.0)	21	(84.0)
No	22	(91.7)	5	(83.3)	2	(40.0)	4	(16.0)
Microcalcification								
Yes	10	(41.7)	0	(0.0)	0	(0.0)	4	(16.0)
No	14	(58.3)	6	(100.0)	5	(100.0)	21	(84.0)

eosinophilic cytoplasm, rasinoid nuclei, and coarsely clumped chromatin pattern (Fig. 2A).

Classical ROs showed densely eosinophilic cytoplasm, smooth to intermediately irregular nuclear membrane, mild to moderate nuclear pleomorphism, finely clumped chromatin pattern, and stromal hyalinization (Fig. 2B). In addition, neither perinuclear halo nor distinct cytoplasmic membrane was observed in C-ROs.

Both E-ChRCs and RO-OHs were characterized by densely eosinophilic cytoplasm, lack of perinuclear halo, and lack of prominent cell border. Nuclear pleomorphism or chromatin pattern was inconsistent. However, there were no microscopic features that could discriminate E-ChRCs from RO-OHs (Fig. 2C and D).

3.3. Nuclear morphometry

The nuclear morphometric features of the disease groups are summarized in Table 3. The NND, SD, and DR were significantly different between C-ChRCs and C-ROs, whereas AR and LD were not significant.

The NND was larger in C-ChRCs (11.47 ± 1.64 μm) than in C-ROs (8.15 ± 1.40 μm) ($P < .01$). A significant difference was also found between E-ChRCs and C-ChRCs. However, it was not different between E-ChRCs and RO-OHs (Fig. 3A). The SD was larger in C-ROs (5.32 ± 0.66 μm) than in C-ChRCs (4.87 ± 0.59 μm) ($P = .02$). In addition, it was similar in E-ChRCs and RO-OHs (Fig. 3B). The DR was significantly larger in C-ChRCs than in C-ROs. The DR was also significantly different between C-ChRCs and E-ChRCs and between RO-OHs and C-ROs, respectively (Fig. 3C). Post hoc analysis by the Mann-Whitney U test indicated that none of the 5 investigated variables could distinguish E-ChRCs from RO-OHs (Table 3). Multivariate logistic regression analysis showed that tumors with NND more than 9.0 μm were more likely to be C-ChRC than C-RO (odds ratio, 42.91; 95% confidence interval, 3.63-506.66).

4. Discussion

It is difficult to tell the difference between E-ChRCs and RO-OHs by histologic examination. There have been many studies to find the immunohistochemical or electron microscopic features to discriminate them [6,7,10,17-20]. In this study, we demonstrated useful microscopic characteristics and nuclear morphometric features of C-ChRCs and C-ROs, and we applied them to differentiate E-ChRCs from RO-OHs.

The diagnostic features of C-ChRCs, such as perinuclear halo, raisinoid nuclear irregularity, and prominent cell boundary, were not found in C-ROs. Although raisinoid nuclei could be observed in C-ROs, they were found in less than 5% of tumor cells. Perinuclear halo was observed in all of the C-ChRCs [21]; however, the perinuclear halo could not be found in any of the E-ChRCs or C-ROs. In low-power field, stromal edema or hyalinization was a very valuable characteristic for ROs. Densely eosinophilic cytoplasm was a typical feature of C-ROs and was observed in a considerable number of both E-ChRCs and RO-OHs [22]. The nuclear and chromatin features of RO-OH were similar to those of C-ChRC; however, the cytoplasmic features of RO-OH were similar to those of C-RO. Although E-ChRCs and RO-OHs were indistinguishable by light microscopic features, some authors demonstrated different electron microscopic features of their mitochondria. Renal oncocytomas revealed uniform and round mitochondria with lamellar cristae, whereas E-ChRCs showed pleomorphic mitochondria with tubulevesicular cristae [22]. Although electron microscopic study is a criterion standard to discriminate, it is not feasible to use in practice because it is costly and time-consuming. Unlike some author's study, nuclear features of bi- or multinucleation, intranuclear inclusion, and microscopic calcification or necrosis were observed in C-ChRCs as well as C-ROs [23]. There was no difference in nucleolar prominence, that is, a component of Fuhrman nuclear grading system, between C-ChRCs and C-ROs.

Nearest nuclear distance was significantly different between C-ChRCs and C-ROs, which is a nearest distance between nuclei of adjacent cells. If there is no stromal edema or overlapping of nuclei, NND will increase as the cell size increases. In addition, NND will increase as the cellular

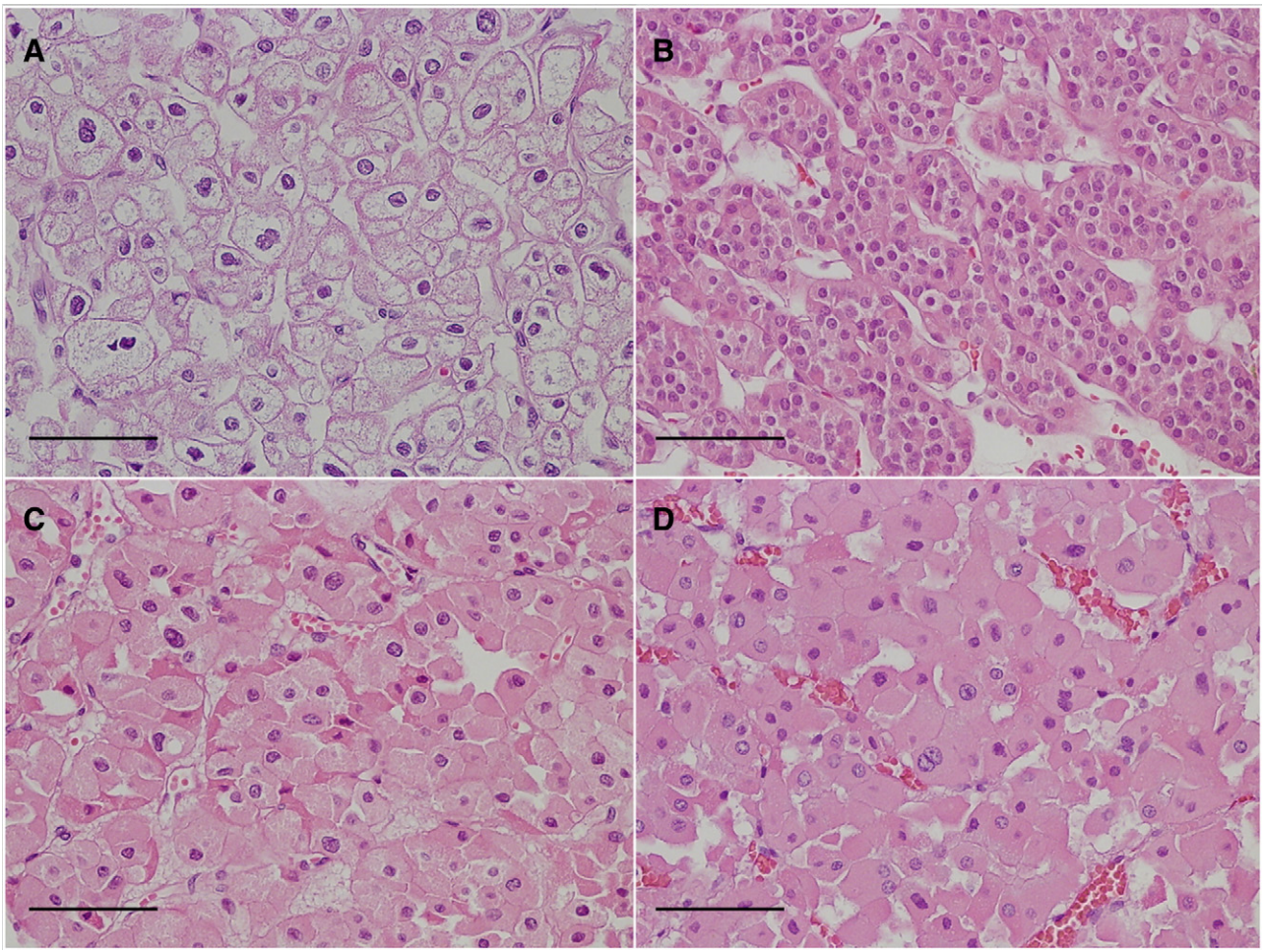

Fig. 2. Representative morphology of C-ChRC (A), C-RO (B), E-ChRC (C), and RO-OH (D). The scale bar represents 100μm.

density decreases. Larger NND means larger cell size and lower cell density. In this study, when NND is larger than 9.0 μm, the tumor is likely to be C-ChRC rather than C-RO. Classical ChRCs showed lower cellular density. Increased cellularity is generally found in malignant rather than benign tumors. It was interesting that C-ROs revealed higher cellular density.

Nuclear diameter ratio is a marker of nuclear roundness. The value is 1.0 for a circle and larger than 1.0 for elliptical structure. The DR of C-RO was smaller than that of C-ChRC. This resulted from the finding that the SD of C-RO was larger than that of C-ChRC, whereas the LD of C-RO and C-ChRC was not different. This finding was in line with the previous finding that C-ROs reveal round and uniform

Table 3
Nuclear morphometric features of renal tumors

	C-ChRC (n = 24)		E-ChRC (n = 6)		RO-OH (n = 5)		C-RO (n = 25)		K-W
	Mean ± SD	CV	Mean ± SD	CV	Mean ± SD	CV	Mean ± SD	CV	*P*
NND (μm)	11.47 ± 1.64	0.14	9.15 ± 1.50	0.16	10.99 ± 2.72	0.25	8.15 ± 1.40	0.17	<.01
M-W	A		B		A, B		B		
LD (μm)	7.49 ± 0.91	0.12	7.29 ± 0.84	0.12	7.74 ± 0.86	0.11	7.18 ± 0.68	0.10	NS
SD (μm)	4.87 ± 0.59	0.12	5.20 ± 0.44	0.08	5.21 ± 0.54	0.10	5.32 ± 0.66	0.12	.02
M-W	A		A, B		A, B		B		
DR	1.61 ± 0.15	0.09	1.45 ± 0.07	0.05	1.55 ± 0.07	0.04	1.40 ± 0.11	0.08	<.01
M-W	A		B, C		A, B		C		
AR (μm^2)	28.94 ± 6.64	0.23	30.01 ± 5.82	0.19	31.90 ± 6.63	0.21	30.29 ± 6.13	0.20	NS

Statistical significance of the difference between groups was tested with the Kruskal-Wallis. The same letters indicate nonsignificant difference between groups based on the Mann-Whitney *U* test ($P > .015$). K-W, Kruskal-Wallis test; M-W, Mann-Whitney *U* test; NS, nonsignificant; CV, coefficient of variation.

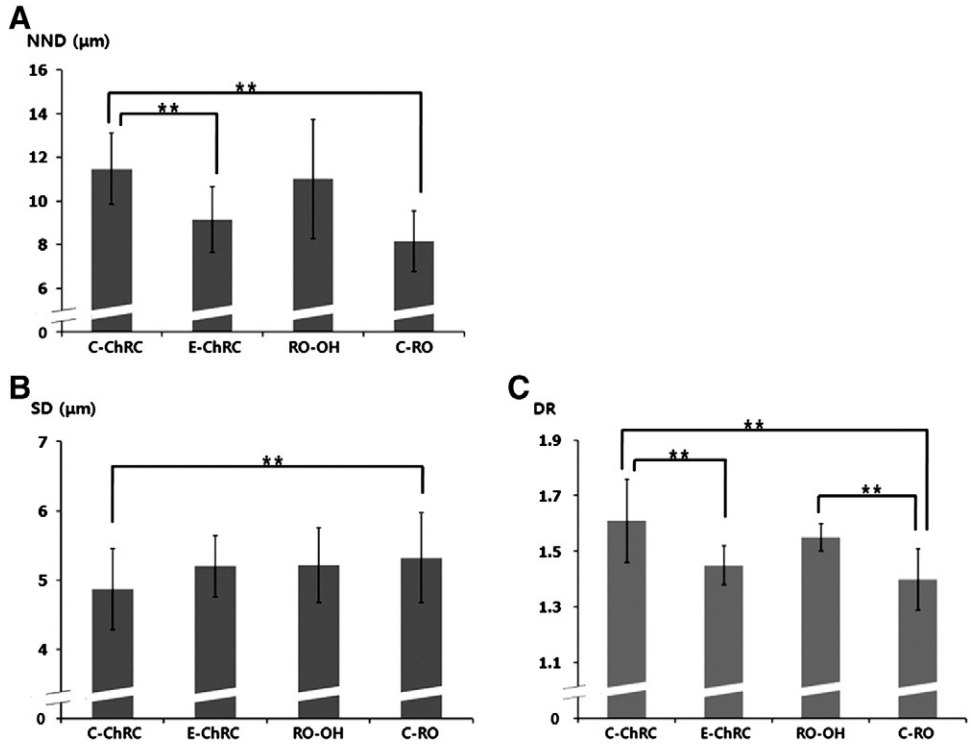

Fig. 3. Values of nuclear morphometric variables. A, The NND is significantly different between C-ChRC and E-ChRC and between C-ChRC and C-RO, respectively. B, The SD is significantly different between C-ChRC and C-RO. C, The DR is significantly different between C-ChRC and E-ChRC, between RO-OH and C-RO, and between C-ChRC and C-RO, respectively.

nuclei [24]. Nuclear diameter ratio was significantly different between C-ChRCs and C-ROs, C-ChRCs and E-ChRCs, and RO-OHs and C-ROs, respectively.

Eosinophilic ChRC and RO-OH showed similar microscopic features. They revealed granular/eosinophilic cytoplasm, inconspicuous nucleoli, lack of perinuclear halo, and lack of distinct cytoplasmic membrane. To differentiate E-ChRCs from RO-OHs, we applied discriminating microscopic features, such as raisinoid nucleus, perinuclear halo, distinct cytoplasmic membrane, and stromal edema/hyalinization as well as nuclear morphometric variables including NND, SD, and DR. However, there was no useful parameter to discriminate them. Therefore, it is necessary to use ancillary studies for making a definitive diagnosis of E-ChRCs and RO-OHs, such as immunohistochemical stain, histochemical stain, or electron microscopic examination [25]. Several biomarkers, such as parvalbumin, MOC31, C-kit, anticaveolin 1, and CK7, would prove useful for the differential diagnosis between E-ChRC and RO-OH. In the previous data, we demonstrated that a panel of immunohistochemical stains for CK7, S100A1, and claudin 8 was valuable for distinguishing C-ChRC from C-RO. We also showed that they could differentiate E-ChRC from RO-OH [12].

In summary, we assessed the microscopic and nuclear morphometric features of C-ChRC, E-ChRC, RO-OH, and C-RO. However, we could not find morphological features that could discriminate E-ChRC from RO-OH.

Acknowledgments

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