

HISTOLOGICAL DIFFERENTIAL DIAGNOSTICS OF RENAL ONCOCYTOMA

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Background: The morbidity rate of kidney cancer has been increasing. Management of patients and their prognosis depend on the specific histological type of tumor. Unfortunately, different renal tumors can have similar histological features, making differential diagnostics challenging. Among the most challenging tasks is differential diagnosis of renal oncocytoma (RO) and chromophobe renal cell carcinoma (ChRCC). **Aim:** To analyze different histological features of renal oncocytomas and specify their pathognomonic characteristics that may be advantageous for the confirmation of the diagnosis. **Materials and Methods:** The medical records and histopathological reports of 197 patients with diagnosis of either RO or ChRCC were analyzed. 37 histological parameters were then evaluated and their prevalence in RO or ChRCC was compared by performing a contingency table analysis. Odds ratio was also calculated. **Results:** The most common growth patterns of ROs were solid (53%), nested (47%), cystic (29%), and alveolar (28%). A combination of two or more growth patterns was seen in 82% of cases mostly composing of nested, cystic, alveolar or solid structures. Most tumors exhibited granular inclusions (70%) and dense cytoplasm (58%). **Conclusion:** With more than 95% confidence, the nested pattern, myxoid stroma, granular cytoplasm and round nuclei are likely indicative of RO, whereas the varying nuclear size, raisinoid nuclei and reticular cytoplasm indicate higher likelihood of ChRCC. Therefore, these features should be analyzed for RO confirmation. **Key Words:** renal oncocytoma, kidney cancer, differential diagnostics, chromophobe renal cell carcinoma, renal tumors with eosinophilic appearance.

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In Ukraine, renal tumors are among the top ten most prevalent malignant neoplasms representing 4.1% of all tumors in male patients and leading to death in 3.5% of cases [1]. Approximately 20% of small kidney tumors are benign and do not require any specific treatment. Renal tumors such as papillary adenoma, renal oncocytoma (RO), and most angiomyolipomas do not, indeed, possess metastatic potential. It is not possible to identify radiologically the specific type of renal tumor. In those cases, percutaneous needle biopsies allow for the proper identification of malignant or benign tumors, except in the case of eosinophilic malignant tumors [2]. Those tumors that are benign are often misidentified as RO due to their RO-like appearance [3]. It is challenging for a pathologist to differentiate appropriately between RO and chromophobe renal cell carcinoma (ChRCC) [3, 4]. The histological similarity of RO and ChRCC resides in that they can both be composed of large and highly differentiated cells with granular eosinophilic cytoplasm. Most scientists explain this eosinophilic appearance by the presence of multiple mitochondria in the cytoplasm [5]. Despite some macroscopical, microscopical and ultrastructural differences, histochemical and immunohistochemical methods are usually required in order to be confident in the correct diagnosis. Both tumors belong to the select group of small renal tumors where accurate diagnosis significantly affects the necessity and extent of the surgical treatment [4].

The aim of our study was to analyze different histological features of RO and to specify their pathognomonic characteristics that may be advantageous for the confirmation of the diagnosis.

MATERIALS AND METHODS

In our study, we analyzed medical records and histopathological reports of patients who were treated surgically in the Institute of Urology and Kyiv Clinical Oncological Center from 1999 to 2016. We were able to retrieve and analyze the case histories for 64 patients (48 of which were diagnosed with RO and 16 with ChRCC).

In order to estimate the tumor size we computed a size index (SI) by multiplying the observed width and height of the tumor. Under the assumption that most of these tumors exhibit a similar shape, this helps us to rank the tumors by size properly without resorting to compute the precise integral of the area.

Additionally, histological postoperative materials for 197 patients with initial diagnoses of either RO or ChRCC were analyzed. The specimens were stained with hematoxylin and eosin. The diagnosis was confirmed by two independent pathologists. The tissues analyzed in this paper are solely those where both pathologists independently arrived at the same diagnostic conclusion (n = 166).

37 histological features were observed for each one of the aforementioned tissues, including characteristics such as the pattern of the tumor growth, the presence of necrosis and hemorrhages, the parameters of stroma, the presence of capsule, the presence and type of inflammatory reaction, and cytological features.

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Abbreviations used: ChRCC – chromophobe renal cell carcinoma; CT – computer tomography; RO – renal oncocytoma; SI – size index.

We compared the prevalence of these features across confirmed cases of RO and ChRCC by performing a contingency table (also known as KxM) analysis using the chi-square probability distribution with one degree of freedom and determined *p*-value corresponding to the null hypothesis that both tumors exhibit each feature to the same degree. We computed the odds ratio in order to assess the magnitude of the difference between the features and 95% confidence interval.

Finally, as a result of the KxM analysis and the odds ratio analysis, we identified seven features that are statistically significant and can be used for differential diagnostics.

RESULTS

From all patients with a confirmed diagnosis, 26% (43/166) of them had a diagnosis of ChRCC and 74% (123/166) had a diagnosis of RO. On the clinical data, which was available for 49 confirmed RO patients, we analyzed the age and gender prevalence, clinical symptoms, kind of the surgical treatment, localization of the tumor, tumor size, and macroscopical features.

Clinical data. Female to male ratio of patients with RO was 1:1.13. Patient’s age ranged from 37 to 84 years, with an average of 59.2 years (male 57.7; female 60.9). RO was asymptomatic in 53% of cases while 36.7% of patients had pain in flanks, 8.2% experienced uncomfortable feelings in the flank, and 2% experienced hematuria. We did not observe any cases of unmotivated weight loss. All patients had surgical treatments with either radical nephrectomy (55.1%), resection of their kidney (34.7%), or tumor enucleation (10.2%). In 51% of patients the tumor was localized on the right side while in 46.9% of patients, the tumor was localized on the left side. In 2.0% of them, the tumor was bilateral and multifocal in the left kidney. As per the results of the computer tomography (CT) and ultrasound on 41 patients, 26.8% of ROs were localized in the lower segment of the kidney, 26.8% — in the medium segment, 19.5% — in the upper segment. 24.4% of tumors were localized between the upper and medium segments and 2.4% — between medium and lower segments.

Additionally, we analyzed the tumor size using data from CT, ultrasound and the macroscopical examination of the postoperative material. The average diameter of RO was 4.78 cm in ultrasound, 5.23 cm in CT, and 4.34 cm by the macroscopical measurement. We computed SI, which results from multiplying the observed width and height of the tumor material (Table 1). As per ultrasound examination (*n* = 30), SI ranged from 3.29 cm² to 73.13 cm²; in CT (*n* = 22), SI ranged from 3.8 cm² to 88.0 cm². Lastly, through macroscopical examination (*n* = 47), the SI ranged from 2.0 cm² to 81.0 cm².

Macroscopically, the color of tumors, the presence of hemorrhages, the areas of cystic degeneration and the presence of central stellate scars were analyzed, among 43 specimens that could be observed for color, most of them (65.1%) exhibited brown color, a significant portion of them were yellow (25.6%), and to a lesser extent, mahogany brown (7.0%) and pink (2.3%). Among 47 specimens where we obtained these data, we observed that 38.3% of cases exhibited macroscopically noticeable hemorrhages. Central stellate scars were present in 14.9% of cases, and cystic degeneration was present in 12.8% of cases.

Histological data. Microscopically, we analyzed the following features of the ROs: growth patterns, presence of hemorrhage and necrotic areas, characteristics of the stroma of the tumor, and its cytological features.

The most common growth patterns of ROs were, in decreasing order, solid (53%), nested (47%), cystic (29%), alveolar (28%), tubular (23%), glandular (15%), trabecular (14%) and papillary (9%) patterns (Fig. 1, 2). No sarcomatoid areas were found in RO samples. A combination of two or more growth patterns was seen in 82.11% of cases, mostly composed of nested, cystic, alveolar or solid structures. We found hemorrhages in 53% of ROs and necrotic areas in 11% of cases.

In terms of stromal characteristics, we looked for the presence of hyalinosis, myxoid areas, presence of capsules around the tumors, fibrosis in tumor

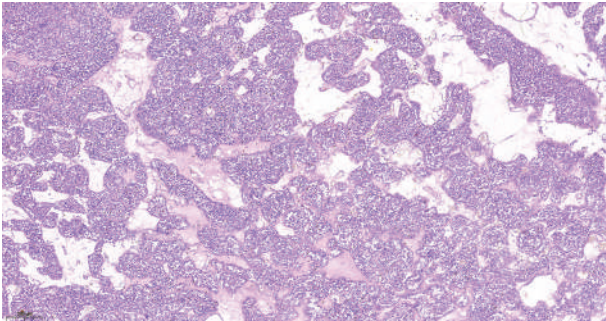


Fig. 1. RO with nested growth pattern and myxoid stroma. Hematoxylin-eosin, × 5.7

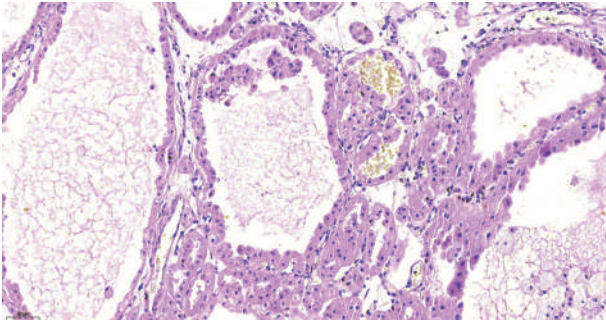


Fig. 2. RO with cystic features, round nuclei and granular cytoplasm. Hematoxylin-eosin, × 20.6

Table 1. SI according to imaging modalities or macroscopic measurement of resected specimen

Observational device	Minimum, cm ²	Maximum, cm ²	Average, cm ²	Median, cm ²	Sample size (n)
Ultrasound	3.29	73.13	25.25	19.06	30
CT	3.80	88.00	30.53	21.63	22
Macroscopical measurement of postoperative specimen	2.00	81.00	22.33	13.50	47

tissues, calcification, presence of adipocytes, and inflammation (Table 2).

Cytologically, we analyzed the features of the cytoplasm of tumor cells as well as nuclear characteristics such as nuclear form, visible in 100x magnification nucleoli, chromatin granularity, hyperchromic nucleus, the prevalence of varying nuclear size and nuclear vacuolization (Fig. 3, 4).

Most tumors exhibited granular inclusions in cytoplasm (70%) and dense cytoplasm (58%). In rare cases, cytoplasm reticularity (5%) and clear cell areas (3%) were seen. The majority of the tumors exhibited round nuclei (86%); less common were tumors with a polygonal (39%) and oval (18%) nuclei. There were no coffee bean-like nuclei in any of the cases of RO in our study. Nucleoli were seen in 28% of cases. Most ROs exhibited nuclear granularity (55%) and hyperchromatic nuclei (53%). Differing size of nuclei in one tumor (10%) and the presence of intranuclear vacuoles (6%) were rare.

Statistical analysis. In order to select the histological and cytological feature indicative of RO or ChRCC, we performed a contingency table analysis and odds ratio analysis (Table 3).

Table 2. Stromal characteristics of RO

Feature	Number	%
Hyalinosis	77	63
Myxoid changes	102	83
Capsule	27	22
Partially present		
Present	48	39
Fibrosis	18	15
Calcification	1	1
Lipids	7	6
Inflammation	46	37
Macrophages	2	2
Lymphocytes	41	33
Total	123	100

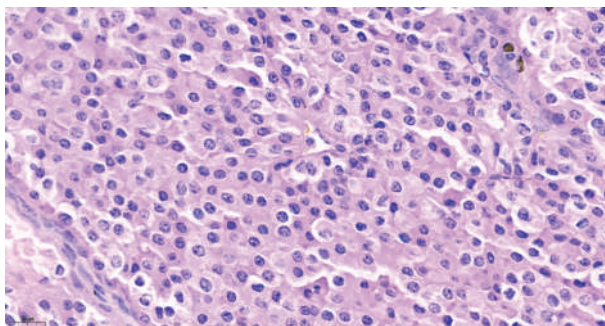


Fig. 3. RO. Tumor cells have granular cytoplasm and round nuclei. Hematoxylin-eosin, $\times 57$

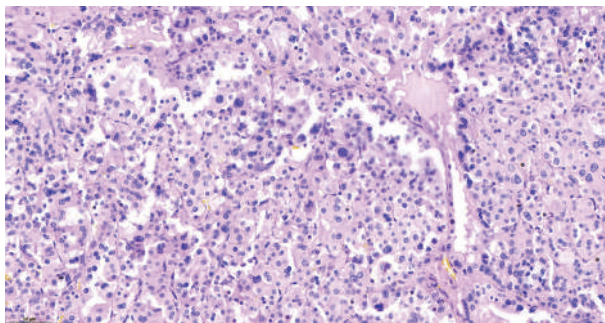


Fig. 4. RO with varying nuclear sizes, which is a feature more typical found in ChRCC. Hematoxylin-eosin, $\times 24.8$

As shown in Table 3 in bold and grey background, the following parameters have p -values below 5% as well as a confidence intervals for the odds ratio that are either entirely below 1 or above 1: nested pattern, myxoid stroma, granular cytoplasm, varying nuclear size, raisinoid nuclei and reticular cytoplasm (Fig. 5). We discarded the results for clear cytoplasm since this feature was found only in 4 RO specimens, which is below the number required (5) for this analysis to be robust.

Therefore, with more than 95% confidence, the nested pattern, myxoid stroma, granular cytoplasm and round nuclei are likely indicative of RO, whereas the varying nuclear size, raisinoid nuclei and reticular cytoplasm indicate higher likelihood of ChRCC.

DISCUSSION

The ROs represent 5–7% of all primary tumors of the renal cortex. RO was described for the first time by Zippel in 1942, and then it was identified as a benign tumor by Klein and Valensi [6]. Mauermann *et al.* [7] described female to male ratio in cases of benign renal tumors as 1.18:1, but when describing ROs, found this ratio to be 1:1.42 ($n = 63$). Our sample, which exhibited a female to male ratio of 1:1.13 was not as heavily skewed towards men, but it nonetheless confirmed the gender bias trend by Mauermann *et al.* [7].

Williams and Lynch [8] stated that RO is most frequently diagnosed in the seventh decade of life. In our research, while the average age observed was 59.2 years old (ranging from 37 to 84 years old), we also found that the most common decade of occurrence of RO was the seventh (39% of all patients).

In study by Dimashkieh *et al.* [6], 5% of ROs were bilateral and 6% of them were multifocal (138 RO cases in total were analyzed). In the present study, with only 49 RO cases, no more than 2% of them were bilateral as well as multifocal.

Macroscopically, ROs are usually brown or mahogany brown, and are well circumscribed [6, 9]. In our study, the majority of RO cases exhibited brown color (65.1%), but mahogany color ROs were uncommon (7%). Of note, color classification is, as of now, highly subjective, so the difference found may not be significant.

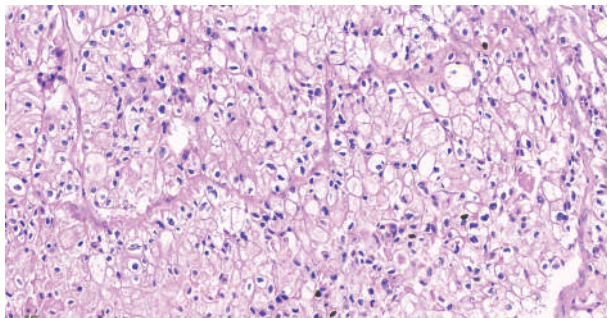
It is worth noting that the presence of central stellate scars has often been considered a characteristic only present in ROs [10]. In our research, we could confirm this finding and, further, estimate the prevalence of central stellate scars in ROs to 14.9% of cases.

Clear cell changes, necrotic areas and papillary growth patterns (excepting areas of dilated tubules) are not typical for ROs. Kryvenko *et al.* [11] stated that these rare clear cell changes could be present only in areas with fibrous scars. All these features were relatively rare in our study as well: clear cell changes were present in 3% of cases, necrotic areas were present in 11% and papillary formations were seen only in 9% of ROs.

Usually, ROs have polygonal cells with abundant cytoplasm and similar round nuclei. Even though rai-

Table 3. Contingency table analysis (KxM) and odds ratio analysis per each indicated feature

Feature	Percentage of ROs,%	Percentage of ChRCCs,%	Chi ² p-value	Odds Ratio	Odd Ratio 95% CI
Calcium deposits	1	0	55.31	N/A	N/A
Tubular pattern	23	5	0.79	6.04	[1.37–26.56]
Nested pattern	47	12	< 0.001	6.78	[2.5–18.39]
Myxoid stroma	83	40	< 0.001	7.43	[3.44–16.06]
Granular cytoplasm	70	37	0.01	3.92	[1.89–8.13]
Capsule is partially present	22	14	25.80	1.73	[0.66–4.54]
Round nuclei	86	56	< 0.001	4.94	[2.24–10.88]
Hyalinosis	63	47	6.54	1.93	[0.95–3.88]
Papillary pattern	9	7	68.96	1.31	[0.35–4.94]
Dense cytoplasm	58	49	31.29	1.43	[0.71–2.87]
Cystic pattern	29	26	64.41	1.20	[0.55–2.65]
Hemorrhage	53	47	47.45	1.29	[0.64–2.58]
Polygonal cells	39	35	63.01	1.19	[0.58–2.46]
Inflammation	37	35	76.84	1.12	[0.54–2.3]
Lymphocytes	33	33	92.59	1.04	[0.49–2.17]
Oval nuclei	18	19	91.61	0.95	[0.39–2.33]
Nuclear hyperchromy	53	56	73.69	0.89	[0.44–1.78]
Capsule is present	39	42	74.36	0.89	[0.44–1.8]
Visible nucleoli	28	30	74.55	0.88	[0.41–1.89]
Solid pattern	53	58	54.86	0.81	[0.4–1.63]
Alveolar pattern	28	33	61.16	0.82	[0.39–1.74]
Granular chromatin	55	65	26.11	0.66	[0.32–1.36]
Trabecular pattern	14	19	45.03	0.70	[0.28–1.77]
Macrophages	2	2	76.69	0.69	[0.06–7.85]
Glandular pattern	15	21	33.56	0.65	[0.27–1.58]
Fibrosis	15	23	19.37	0.57	[0.24–1.35]
Necrosis	11	19	17.24	0.52	[0.2–1.35]
Nuclear vacuolation	6	12	19.57	0.46	[0.14–1.53]
Varying nuclear size	10	26	0.97	0.31	[0.13–0.78]
Cigar shaped nuclei	1	2	43.39	0.34	[0.02–5.63]
Fat inclusions	6	16	3.15	0.31	[0.1–0.94]
Giant nuclei	1	5	10.39	0.17	[0.01–1.9]
Raisinoid nuclei	12	72	< 0.001	0.05	[0.02–0.13]
Reticular cytoplasm	5	35	< 0.001	0.10	[0.03–0.27]
Clear cytoplasm	3	40	0.00	0.05	[0.02–0.17]
Sarcomatoid pattern	0	2	8.98	0.00	N/A
Coffee bean shaped nuclei	0	5	1.61	0.00	N/A

**Fig. 5.** Features less likely to be present in ROs: raisinoid nuclei and reticular cytoplasm, shown in a ChRCC tissue. Hematoxylin-eosin, × 26.2

sinoid nuclei are typical for ChRCCs, they are present in less than 5% of cases of ROs [12]. In our RO sample raisinoid nuclei were more common (12%), which unfortunately means that this feature is less differentiating than originally thought.

Some areas of degenerative atypia and absence mitoses in ROs were found [9]. In our study, we found only 1% of giant multinucleated cells.

Interestingly, 10%–30% of ROs can contain areas with renal cell carcinoma so the presence of RO in the sample does not necessarily exclude the presence of renal cell carcinoma as well [6, 9]. In our study, no renal cell carcinoma areas in RO tissue were found.

Therefore, we could be able to delineate the histological and cytological features that could be advantageous for discriminating between RO and ChRCC. The presence of nested pattern, myxoid stroma, granular cytoplasm and round nuclei are likely indicative

of RO while the varying nuclear size, raisinoid nuclei and reticular cytoplasm with higher likelihood are in favor of ChRCC. For confirmation of RO diagnosis, these histological and cytological features should be evaluated. Nevertheless, if the results are still inconclusive, the immunohistochemical analysis should be performed.

In our recent publication, we have analyzed in details the histological characteristics of ChRCC as compared with RO with the aim of defining the predominance of the specified features in these two forms of renal cancer [13]. Based on these findings, the current paper analyzed statistically the significance of each of the histological features under study to delineate the features that are indicative of RO or ChRCC. The present study as well as the preceding one emphasize that the verification of the diagnosis requires the detailed analysis of histological particulars. The further delineation of the optimal histological markers would be an important complementary means for the reliable differential diagnostics.

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