Original Article

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General Overview of Renal Cell Carcinoma with the Evaluation of Our Cases

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ABSTRACT

Objective: Renal cell carcinoma (RCC) is the 14th most common tumor in the world. In 2010, the protocol for the examination of kidney specimens with invasive carcinoma of renal tubular origin was updated. The aim of our study was to review 1-year RCC patients of our hospital according to the new protocol, classification, and staging systems with respect to their morphological and immunohistochemical features.

Methods: The medical records of 54 RCC patients between July 2012 and July 2013 were retrospectively reviewed. They were classified according to the WHO 2004 classification system and newly defined subtypes. The following variables were determined in each case: age, sex, histological subtype, stage, and Fuhrman nuclear grade.

Results: In our study, 30 (55.6%) men and 24 (44.4%) women were diagnosed with RCC out of 54 patients. The median age was 56 years. In total, 21 patients had (55.2%) right- and 17 had (44.74%) left-sided tumors. Thirty-eight (70.3%) clear cell, 6 (11.1%) papillary, 7 (12.96%) chromophobe, 1 (1.85%) multilocular, 1 (1.85%) unclassified, and 1 (1.85%) tubulocystic RCC were seen. According to primary tumor, 33 (61.1%) pT1, 10 (18.51%) pT2, 9 (16.66%) pT3, and 2 (3.70%) pT4 patients were reported. Chromophobe RCCs were excluded from the Fuhrman grading (G) system; of the remaining 2 (4.17%) were G1, 30 (62.5%) were G2, 13 (27.08%) were G3, and 3 (6.25%) were G4 tumors.

Conclusion: Although RCC constitutes the majority of renal tumors, different subtypes are also encountered. In our study, clear cell RCCs were the most common type of tumors consistent with the literature. The remarkable point was that chromophobe RCCs were more frequent in our study. Because of infrequency, more examples are required to distinguish newly defined subtypes.

Keywords: Renal cell carcinoma, staging, subtype

Introduction

The incidence of kidney tumors is 2% among all cancers, and approximately 190,000 new cases are diagnosed every year (1). According to the 2004 World Health Organization (WHO) report, kidney tumors are histopathologically classified as renal cell tumors, mesonephric tumors, nephroblastic tumors, neuroendocrine tumors, neuroblastoma, pheochromocytoma, and other tumors (1). Renal cell carcinoma (RCC) is the most common type and it ranks 13th in the world and 10th in Europe in the classification of the most common cancers in the world (2). According to WHO, RCCs are mainly divided into subtypes, such as clear cell, papillary, chromophobe, collecting duct, mucinous tubular and spindle cell, medullary, translocation-associated, neuroblastoma-associated, and unclassified (1, 3). In addition to the identification of histopathological new subtypes, some changes have also been made in the staging of RCC in recent years, the staging protocol being renewed in 2010 (4, 5). Moreover, the International Society of Urological Pathology (ISUP) published the Vancouver classification for renal tumors in 2013 (6). In addition to the classification of WHO, the addition of the Vancouver classification subtypes, tubulocystic, acquired cystic related disease, clear cell (tubulo) papillary, MIT

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family translocation t(6; 11) associated RCC, hereditary leiomyomatosis RCCs, newly developed thyroid-like follicular carcinoma of the kidney, carcinoma associated with succinate dehydrogenase B deficient RCCs, and ALK translocation RCCs, to the classification of 2004 WHO RCCs is on the agenda (6).

Although many RCC subtypes are distinguished through histomorphological examination, immunohistochemical studies help distinguish the tumors in cases with difficulties in diagnosis, especially in clear cell, eosinophilic granular cytoplasm, and papillary tumors (6, 7).

Detection of CD10, RCC positivity, CK7, and α-methyl acyl-CoA racemase (AMACR) negativity for clear cell RCC;PAX8, vimentin, CD10, AMACR, CK7, and occasionally observed RCC positivity for papillary RCC;CK7, CD117 positivity, and vimentin and CD10 negativity for chromophobe RCC;CK7, CaIX positivity, and AMACR and CD10 negativity for clear cell (tubulo) papillary RCC; AE1/AE3, high molecular weight keratin (HMWK), PAX8, CD10, GATA3 positivity, and p63 negativity for collecting duct carcinoma help in the immunohistochemical diagnosis (6).

This study was planned to review malignant renal tumors submitted to our pathology department in the past year, to determine histopathological diagnosis spectra through the new classification system and immunohistochemical stains, and to reassess the patients according to histological grade and the new staging system.

Methods

Fifty-four nephrectomy material sent to our Pathology department, between July 1, 2012- July 1, 2013, were included in the study. After the age, sex, tumor localization, and tumor diameter data were collected, histopathological diagnosis was made according to WHO 2004 classification. Only the malignant tumors originating from renal tubular were included in the study and urothelial cancers and benign tumors were excluded. The patients were re-evaluated according to Fuhrman nuclear grading and stage. RCC (monoclonal, clone 66.4.C2, Scytec, Greenwood Village, USA), vimentin (monoclonal, clone V9, BioGenex Milmont Dr, Fremont, CA), CD10 (monoclonal, clone 56C6, BioGenex Milmont Dr, Fremont, CA), CD15 (monoclonal, clone MMA, Thermo A63, Waltham, Massachusetts, USA), E-cadherin (monoclonal, clone A36, BioGenex, Milmont Dr, Fremont, CA), CD117 (monoclonal, clone YR145, BioGenex Milmont Dr, Fremont, CA), cytokeratin 7 (monoclonal, clone OV-TL12/30, BioGenex Milmont Dr, Fremont, CA), cytokeratin 20 (monoclonal, clone KS20.8, Thermo, Waltham, Massachusetts, USA), cytokeratin 19 (monoclonal, clone RCK108, BioGenex, Milmont Dr, Fremont, CA), AMACR (monoclonal, clone 131+4, BioGenex, Milmont Dr, Fremont, CA), MUC1 (monoclonal, clone MRQ 17, Cell Marque, Rocklin, California, USA), and HMWK (monoclonal, clone 34β12, Scytec, Greenwood Village, USA) stains had been immunohistochemically applied (with Ventana Benchmark XT-USA device) in 24 cases in which no clear diagnosis was made histopathologically, and these stains were reviewed.

Statistical analysis

In our study, the distribution of the subtypes and tumor types of RCCs according to the TNM classification is given as percentage.

Results

Of the nephrectomy materials, 34 (63%) were partially and 20 (37%) were radically excised. Of the 54 RCC patients, 30 (55.6%) were men and 24 (44.4%) were women, with the average age being 56 years. Of the tumors, 21 (55.26%) were located on the right and 17 (44.74%)

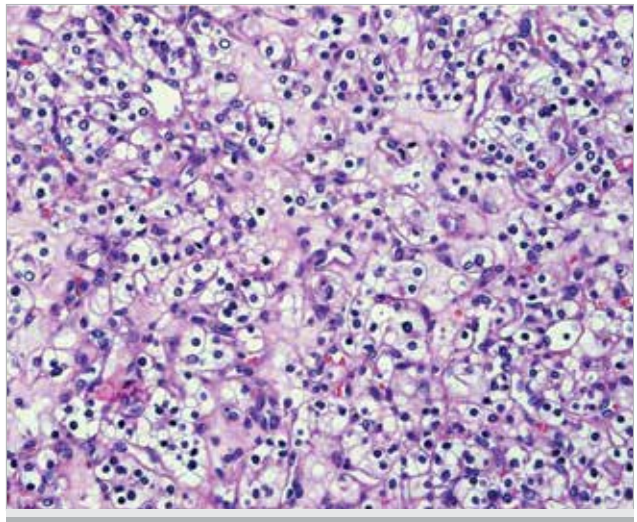

Figure 1. Clear cell carcinoma (H-EX200)

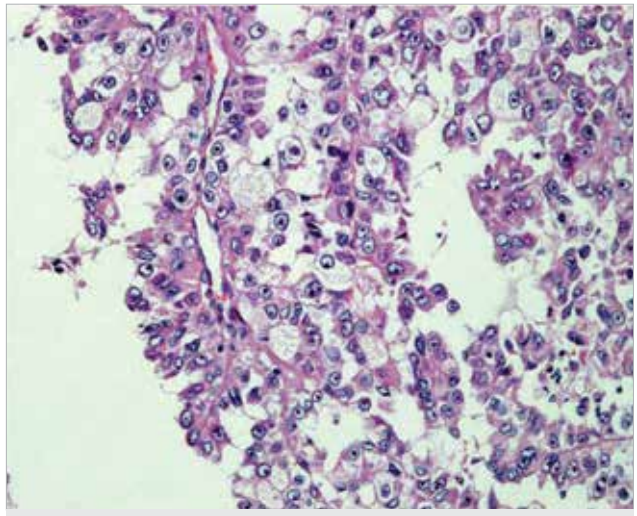

Figure 2. Papillary renal cell carcinoma (H-EX200)

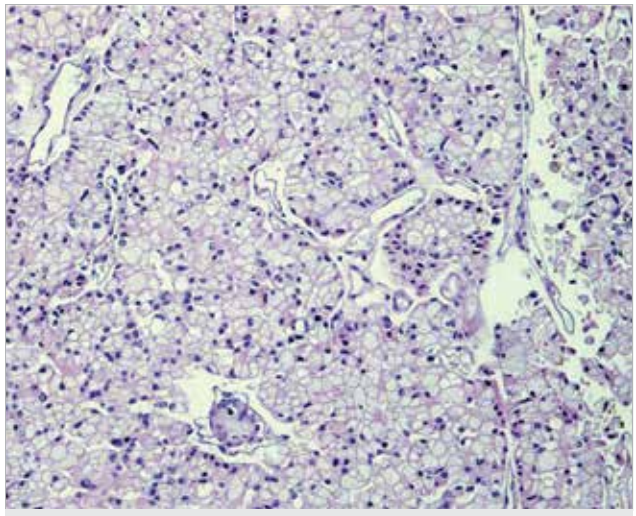

Figure 3. Chromophobe renal cell carcinoma (H-EX100)

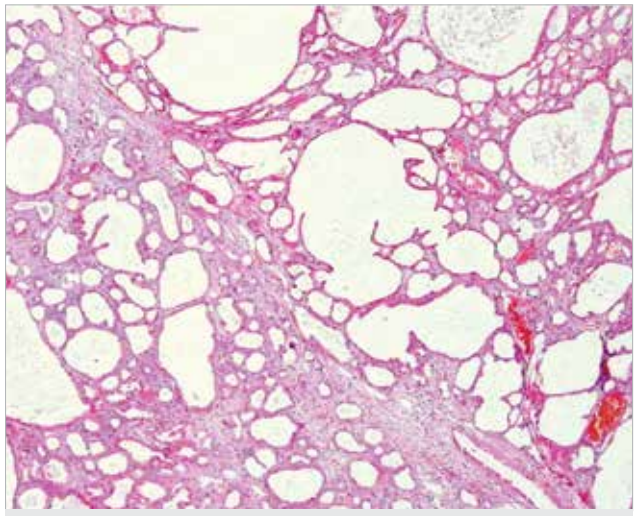

Figure 4. Tubulocystic carcinoma (H-EX100)

on the left. Mean tumor diameter of the partial nephrectomies was 5 cm and that of the radical nephrectomies was 8.5 cm, with an average diameter of 6.4 cm for all nephrectomies. Of the cases, 38 (70.35%) were classified as clear cell RCC (Figure 1), 6 (11.1%) were papillary (Figure 2), 7 (13%) were chromophobe (Figure 3), 1 (1.85%) was multilocular, 1 (1.85%) was tubulocystic (Figure 4), and 1 (1.85%) was unclassified (Figure 5). Sarcomatoid features were observed only in 2 (3.70%) patients (Table 1). In the evaluation according to the Fuhrman nuclear grading system (G) in tumors other than those classified as chromophobe cell RCC, 2 (4.17%) of the cases were G1, 30 (62.5%) were G2, 13 (27.08%) were G3, and 3 (6.25%) were G4. As a result of the pathological staging, 33 (61.1%) of tumors were pT1, 10 (18.53%) were pT2, 9 (16.67%) were pT3, and 2 (3.70%) were pT4 (Table 2).

In the histopathological examination of 7 cases, chromophobe RCC and oncocytoma were included in the differential diagnosis in tumors with large eosinophilic

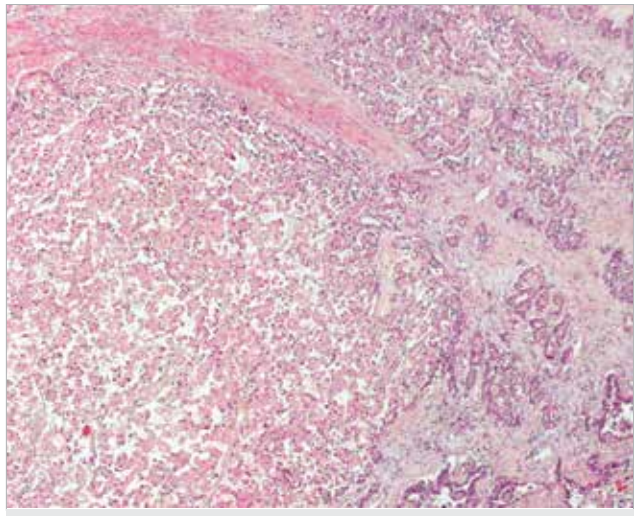

Figure 5. Unclassified RCC, transition of, chromophobe cell carcinoma, and collecting duct carcinoma (H-EX40)

Table 1. The distribution of subtypes of RCC

Diagnosis	Number of cases	%
Clear cell RCC	38	70.35
Papillary RCC	6	11.1
Chromophobe RCC	7	13
Multilocular BCC	1	1.85
Collecting duct carcinoma	0	0
Medullary carcinoma	0	0
Mucinous tubular and spindle RCC	0	0
Translocation-associated RCC	0	0
Neuroblastoma-associated RCC	0	0
Unclassified RCC	1	1.85
Tubulocystic RCC	1	1.85
Clear cell papillary RCC	0	0
Thyroid-like follicular RCC	0	0
Hereditary leiomyomatosis-associated RCC	0	0
Acquired cystic disease-associated RCC	0	0
Succinate dehydrogenase-deficient RCC		

RCC: renal cell carcinoma

cytoplasm, separated by distinct boundaries from each other, some of which had raisinoid nucleus with perinuclear halo. A central scar, commonly observed in oncocytomas, was not observed in others. Oncocytoma was excluded as a result of immunohistochemical staining with cytokeratin 7 (Figure 6), CD117, E-cadherin positive, cytokeratin 20, CD15, and negative staining of RCC, and the cases were defined as chromophobe RCC.

Table 2. The distribution of tumor types according to TNM classification

	Clear	Chromophobe	Papillary	Multilocular	Tubulocystic	Unclassified	
TNM stage	1a	14 (%26)	3 (%5.5)	2 (%3.7)			
	1b	9 (%17)	2 (%3.7)	2 (%3.7)		1 (%1.85)	
	2a	2 (%3.7)		1 (%1.85)	1 (%1.85)		
	2b	3 (%5.5)	1 (%1.85)	1 (%1.85)			1 (%1.85)
	3a	6 (%10.85)	1 (%1.85)				
	3b	1 (%1.85)					
	3c	1 (%1.85)					
	4	2 (%3.7)					

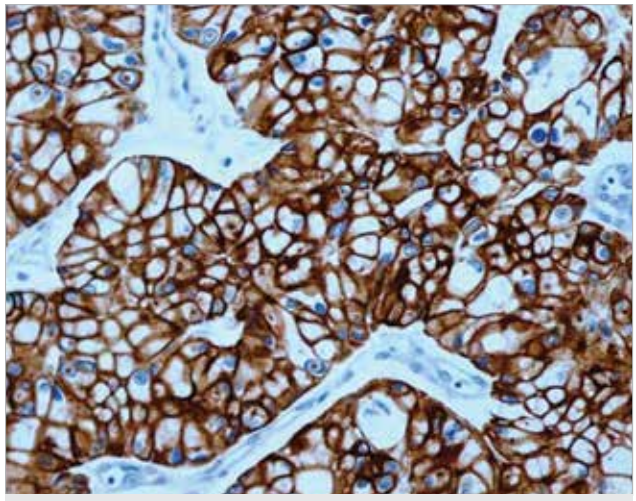

Figure 6. The positivity of cytokeratin 7 in chromophobe renal cell carcinoma (x200)

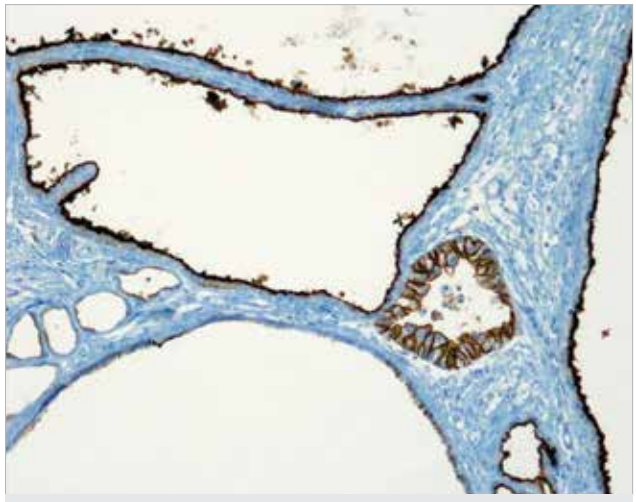

Figure 7. The positivity of CD10 in tubulocystic carcinoma (x100)

One tumor had spongy areas in its cut surface. On histopathological examination, it consisted cysts and tubules of different sizes, seperated by thin septa covered by thin single row cubic and in some areas hobnail-shaped

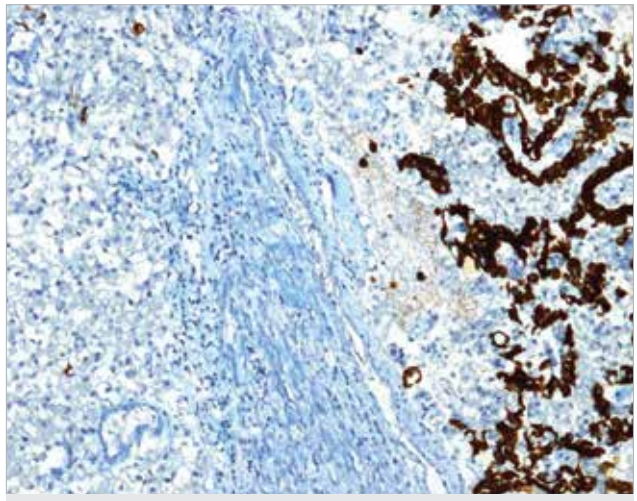

Figure 8. In unclassified renal cell carcinoma, while CK19 was negative in the area of chromophobe cell carcinoma, it was positive in the area of collecting duct carcinoma (H-EX100)

epithelium. The cells had large eosinophilic cytoplasm and prominent nucleoli with regular core. Multi-cystic RCC, cystic nephroma, mixed epithelial tumor, and tubulocystic carcinoma were included in differential diagnosis. Immunohistochemical staining showed a diffuse positivity with CD10 (Figure 7), AMACR, cytokeratin 19, and vimentin and focal positivity with cytokeratin 7 and HMWK. The case was reported as tubulocystic carcinoma using immunohistochemical analysis. In addition to the fact that the tumor neither had morphologically clear cells as in multi-cystic RCC, nor had a structure similar to ovarian or fibrotic stroma as in cystic nephroma. Also it did not contain 2 different components as in mixed epithelial tumor.

In all, 6 cases were histopathologically shown to be composed of papillary and tubular structure, and the papillary structures had a fibrovascular stalk. The epithelial lining was in a single row in some areas and focally had pseudostratification. In some cases, foamy histiocytes were noted among cells. With the help of AMACR and CD15 positivity, they were diagnosed as papillary RCC.

In 1 case, there were structures that suggested different types of carcinoma such as chromophobe, papillary, and collecting duct carcinoma. Immunohistochemical analysis showed that the cells were positive for cytokeratin 7, MUC1, cytokeratin 19 (Figure 8), and HMWK focal and negative for RCC, CD68, and CD 10. The discrimination of subtype could not be made by histopathological and immunohistochemical findings. This patient was finally reported as unclassified type of RCC. Clear cell RCC, had solid islands, alveolar and aciner patterns. They had large number of thin walled vascular structures,and microcysts lined by clear cells. This tumors showed RCC and CD10 positivity.

Discussion

The incidence of RCC increases by a rate of 2-4% every year and ranks highest in deaths due to genitourinary cancers (8). According to the values of the European Association of Urology, the male/female incidence ratio is 1.5, and it was most common in the fifth and sixth decades. The female/male incidence ratio among our patients was 1.25, and the mean age was 56 years. Our findings are consistent with those in the literature (9). While the rate of the partial nephrectomy application to renal cortical tumors of ≤4 cm was 7.5% in the study of Russo et al. between the years 1988 and 2002 in the United States, it was reported that this ratio rose to 60-70% in a study conducted in 2008. In the same study, the rate of partial nephrectomy was mentioned to be 4% in the UK in 2002; when compared with this value, we can say that the rate of partial nephrectomy in our hospital is at an ideal level (10).

Although RCCs constitute a majority of renal tumors, we also encounter other subgroups from time to time. Clear cell carcinomas are tumors with a thin vascular network having clear or eosinophilic cytoplasm. Papillary tumors are malignant tumors forming papillary and tubular structures at different rates. Chromophobe RCCs are tumors that are composed of large polygonal cells, are transparent, and have light reticular cytoplasm and distinct cell membranes (3). Of the most common RCCs, 80-90% are clear cell, 10-15% are papillary, and 4-5% are chromophobe RCCs (8). Consistent with the literature, RCC was identified as the most common tumor in our study. However, chromophobe cell RCCs were more common in our study than in the literature, with a percentage close to papillary RCC. Sarcomatoid alteration was only observed in 2 patients with clear cell carcinoma and this is in line with the <5% incidence in the literature (11, 12).

Unclassified RCC is a rare type with a form that does not conform to any histological subtype, and it can also be seen as a combination of different structures, and is encountered at a rate of 4-6% (13). The only unclassified case in our study was the coexistence of different types that had areas suggesting chromophobe, papillary, and collecting duct carcinoma. The case was diagnosed as unclassified RCC because it showed no compatibility with any histological subtypes in the literature.

Among the tumors to be added in the new classification, tubulocystic carcinoma suggests the presence of tumors that macroscopically consist of cysts of varying diameters, have a spongy appearance, On microscopic examination the cysts were coverd by cubic and hobnail shaped epithelium in a single row (13). Immunoreactivity is usually observed with CD10, AMACR, parvalbumin, and CK19. In the literature, 3 series of 11, 13, and 31 cases have been reported so far (14). Because 1 of the tumors in our 1-year series showed similarity to these histopathologically and immunohistochemically defined features, it was interpreted as tubulocyctic carcinoma.

In the study of 151 RCC cases conducted by Yap et al. (15) and published in 2014, 11.6% of the patients were reported as G1, 52.6% as G2, 25.3% as G3, and 10.5% as G4. The difference among the rates was explained by noncompliance among the evaluators.

In 2010, AJCC/UICC made changes in the staging of RCC in comparison to the 2002 classification. These changes are the separation of pT2 group as pT2a (tumor diameter 7-10 cm) and pT2b (tumor diameter >10 cm), putting the presence of thrombus in renal vein or branches to pT3a instead of pT3b, and moving contiguous extension of the tumor into the adrenal gland from pT3a to pT4 (16, 17). The purpose of these changes is to better determine the prognosis of the disease and to organize the schemes of treatment and follow-up accordingly. According to the data of 2010 AJCC/UICC classification of the last 1 year, the majority of our patients were in the group of pT1-pT2.

Although immunohistochemical staining is helpful in diagnosis from time to time, it is also used as a helpful method for differential diagnosis and to identify the rare types. RCCs usually express RCC, CD10, low-molecular-weight keratin, CK19, vimentin, and PAX 2; chromophobe RCC usually express cytokeratin 7, CD117, EMA, and parvalbumin; and the papillary RCC cases often express cytokeratin 7, AMACR, CD15, CD10, RCC, and MUC 1 (3, 18, 19). Staining characteristics compatible with the literature were often observed with the immunohistochemical stains applied to our patients. We believe that the large panel of immunohistochemical stains applied in suspected cases contributed to the reporting of chromophobe RCCs in our cases a little more than that in the literature. In addition, immunohistochemistry contributed to the diagnosis of subtypes that are rarely seen or newly defined and also seen in our

annual series. Our unclassified RCC showed a different staining behavior according to the components that it contained as described in the literature.

Conclusion

Renal tumors have an important place in the routine of pathology. Both histopathological classification and correct staging are important in the prognosis and treatment of the patient. Immunohistochemistry performed with large panels is helpful both in differential diagnosis and determining subtypes. Studies with large series in different centers would be helpful to determine the frequency of RCC's subtypes.

Ethics Committee Approval: Ethics committee approval was not received due to the retrospective nature of the study.

Informed Consent: Informed consent was not obtained due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

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References

1. Eble JN, Sauter G, Epstein JI, Sesterhenn IA, editors. World Health Organization classification of tumours. Pathology and genetics tumours of the urinary system and male genital organs. Lyon, France: IARC Press; 2004.
2. Ljungberg B, Campbell SC, Choi HY, Jacqmin D, Lee JE, Weikert S, et al. The epidemiology of renal cell carcinoma. Eur Urol 2011; 60: 615-21. [CrossRef]
3. Lopez-Beltran A, Scarpelli M, Montironi R, Kirkali Z. 2004 WHO classification of the renal tumors of the adults. Euro Urol 2006; 49: 798-805. [CrossRef]
4. Algaba F, Akaza H, López-Beltrán A, Martignoni G, Moch H, Montironi R, et al. Current pathology keys of renal cell carcinoma. Eur Urol 2011; 60: 634-43. [CrossRef]
5. Moch H, Artibani W, Delahunt B, Ficarra V, Knuechel R, Montorsi F, et al. Reassessing the current UICC/AJCC TNM staging for renal cell carcinoma. Eur Urol 2009; 56: 636-43. [CrossRef]
6. Srigley JR, Delahunt B, Eble JN, Egevad L, Epstein JI, Grignon D, et al. The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia. Am J Surg Pathol 2013; 37: 1469-89. [CrossRef]
7. Shen SS, Truong LD, Scarpelli M, Lopez-Beltran A. Role of immunohistochemistry in diagnosing renal neoplasms: when is it really useful? Arch Pathol Lab Med 2012; 136: 410-7. [CrossRef]
8. Cairns P. Renal cell carcinoma. Cancer Biomark 2011; 9: 461-73.
9. Ljungberg B, Cowan NC, Hanbury DC, Hora M, Kuczyk MA, Merseburger AS, et al. EAU guidelines on renal cell carcinoma: the 2010 update. Eur Urol 2010; 58: 398-406. [CrossRef]
10. Russo P, Huang W. The medical and oncological rationale for partial nephrectomy for the treatment of T1 renal cortical tumors. Urol Clin North Am 2008; 35: 635-43. [CrossRef]
11. Pradhan D, Kakkar N, Bal A, Singh SK, Joshi K. Sub-typing of renal cell tumors; Contribution of ancillary techniques. Diagn Pathol 2009; 4: 21. [CrossRef]
12. Young AN, Amin MB, Moreno CS, Lim SD, Cohen C, Petros JA, et al. Expression profiling of renal epithelial neoplasms:a method for tumor classification and discovery of diagnostic molecular markers. Am J Pathol 2001; 158: 1639-51. [CrossRef]
13. Yıldız K. Böbrek tümörlerinin patolojik sınıflamasında güncel gelişmeler. Üroonkoloji Bülteni 2011; 10: 86-90.
14. Azoulay S, Vieillefond A, Paraf F, Pasquier D, Cussenot O, Callard P, et al. Tubulocystic carcinoma of the kidney: A new entity among renal tumors. Virchows Arch 2007; 451: 905-9. [CrossRef]
15. Yap NY, Ng KL, Ong TA, Pailoor J, Gobe GC, Ooi CC, et al. Clinical prognostic factors and survival outcome in renal cell carcinoma patients--a malaysian single centre perspective. Asian Pac J Cancer Prev 2013; 14: 7497-500. [CrossRef]
16. Özkan TA, Yıldız K, Dillioğlugil Ö. Böbrek hücreli kanser evrelemesi: 2010 TNM sınıflandırma sistemi ve Türkiye geçerliliği. Üroonkoloji Bülteni 2009: 44-8.
17. Edge SB, American Joint Committee on Cancer. AJCC cancer staging manual. 7th.New York: Springer; 2010: 3-26.
18. Skinnider BF, Folpe AL, Hennigar RA, Lim SD, Cohen C, Tamboli P, et al. Distribution of cytokeratins and vimentin in adult renal neoplasms and normal renal tissue: potential utility of a cytokeratin antibody panel inthe differential diagnosis of renal tumors. Am J Surg Pathol 2005; 29: 747-54. [CrossRef]
19. Şen S, Sarsık B, Şimşir A. Immunohistochemical markers in renal tumors and findings in non-tumoral renal parenchyma. Türk Patoloji Derg 2010; 26: 120-9. [CrossRef]