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Original Article

Correlation among different pathologic features of renal cell carcinoma: a retrospective analysis of 249 cases

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Abstract: Renal cell carcinoma (RCC) represents 90% of renal malignancies and is the most lethal neoplasm of the urologic system. RCC is not a single entity but rather a heterogeneous group of neoplasms with varying genetic, morphologic and clinical features and outcome. The aim of this study was to correlate pathologic features of RCC that can be helpful during the decision-making process. We present a retrospective analysis of 249 RCCs (203 clear cell, 32 papillary and 14 chromophobe RCCs). We found that 77.8% of tumors of ≤4 cm and only 28.8% of RCC of >7 cm were limited to the kidney. The likelihood of lymphovascular invasion, fibrous renal capsule/perinephric fat/renal sinus fat, and vascular infiltration increased dramatically with increasing tumor size, particularly over 4.5 cm. Fat tissue was more often invaded through the renal sinus than through the renal capsule. Nuclear grade was significantly related to the pT stage, tumor size, percentage of necrotic area, lymphovascular invasion, fibrous renal capsule/perinephric fat/renal sinus fat and vascular infiltration. Tumor size represents one of the most important factors determining biological behavior of renal cancer. Renal sinus and perinephric fat should be carefully investigated, particularly in case of tumors >4-5 cm. Despite increasing acceptance for partial nephrectomy in tumors >7 cm, these cancers invade renal sinus fat 11 times more often and perinephric fat 5.6 times more often than smaller ones.

Keywords: Renal cell carcinoma, clear cell renal cell carcinoma, papillary renal cell carcinoma, chromophobe renal cell carcinoma

Introduction

Renal cell carcinoma (RCC) represents 2-3% of adult cancers, accounts for 90% of renal malignancies and is the most lethal neoplasm of the urologic system [1]. The median age at diagnosis is 65 years. Males are two to three times as affected as females [2]. Most RCCs are asymptomatic and discovered as unexpected findings on imaging performed for unrelated clinical indications [3, 4]. RCC is not a single entity but rather a heterogeneous group of neoplasms with varying genetic, morphologic and clinical features including outcome [5]. According to the fourth edition of the World Health Organization (WHO) classification of urogenital tumors published in 2016 RCC is stratified into several distinct histologic subtypes of which clear cell (ccRCC), papillary (pRCC), and chromophobe (chRCC) tumors account for 65-70%, 18.5%, and 5-7%, respectively [6]. Every subtype is associated with different biologic behavior, prognosis, treatment options and response to therapy, therefore knowledge of each RCC subtype is important [5, 7].

The aim of our study was to correlate pathologic features of RCC that can be helpful during the decision-making process by the urologists and oncologists dealing with RCC to optimize the treatment.

Materials and methods

We analysed 249 cases of RCC (203 ccRCCs, 32 pRCCs and 14 chRCCs) searched from January 2015 to May 2019 in Department of Pathology, Zabrze, Poland. All patients had been treated with curative intent by partial or radical nephrectomy. In all cases the submitted surgical specimens were handled according to

the current guidelines of the Polish Society of Pathologists and complied with the recommendations of the ISUP and the WHO for specimen handling, sampling, and reporting [8, 9]. Sections from all cases were reviewed by two pathologists who assigned both a WHO/ISUP grade and eighth edition of the American Joint Committee on Cancer (AJCC) TNM pathologic staging category [10]. Sections were then assessed for: morphotype, tumor size, WHO/ISUP grade, the presence of necrosis, sarcomatoid and rhabdoid differentiation, small vessel lymphovascular invasion, neuroinvasion, fibrous renal capsule invasion, perinephric fat invasion, renal sinus fat and vascular invasion of renal sinus vessels, macroscopic main renal vein invasion, and AJCC TNM pathologic stage of the primary tumor (pT) and pathologic stage of lymph node metastases (pN). Invasion of the perinephric fat was evaluated for a total of 249 tumors, while infiltration of the renal sinus only for cases treated by radical nephrectomy, i.e. 142 cancers. In cases of ccRCC we assessed proportion of cells with clear cytoplasm, while pRCC were subtyped as type 1 or 2. In our study all morphotypes were grouped together, but additionally we separated RCC according to the histological subtype for analytical purposes.

Statistical analysis

All analyses were performed using STATISTICA 13 software (Statsoft, USA). Quantitative data was presented as mean ± SD. Shapiro-Wilk W-test was performed to determine distribution of analyzed variables, while Mann-Whitney U-test to establish differences between data items.

To evaluate associations between variables Spearman's rank correlation coefficient was performed. Pearson's chi-squared test was used to determine differences between qualitative variables. *P*-values of <0.05 were considered significant.

Results

Adequate histological material was obtained for all 249 cases of RCC of which ccRCC, pRCC, and chRCC accounted for 203 (81.5%), 32 (12.9%) and 14 (5.6%), respectively. Among 249 patients, 93 (37.3%) were female and 156 (62.7%) were male. The mean age of females was significantly higher than males (65.6 ± 8.6 years vs. 62.6 ± 10.5 years) (P<0.05). The clinical and pathologic characteristics for the cases are detailed in **Table 1**. Among all 249 tumors, 116 (46.6%) RCCs were ≤4 cm, 66 (26.5%) RCCs were >4 cm but ≤7 cm and 67 (26.9%) RCCs were >7 cm in maximum dimension. Whereas, among cases treated by radical nephrectomy 36 (25.4%) RCCs were ≤4 cm, 47 (33.1%) RCCs were >4 cm but ≤7 cm and 59 (41.5%) RCCs were >7 cm.

Histologic features assessed in our study

Pathologic stage of the primary tumor (pT): The likelihood of lymphovascular invasion, fibrous renal capsule/perinephric fat/renal sinus fat and vascular infiltration increased dramatically with increasing tumor size (especially for ccRCC), particularly over 4.5 cm. True pT2 tumors (tumors of >7 cm limited to the kidney) were rare. We observed that the percentage of pT2 tumors, both total RCC and every morphotype, was significantly lower than the percentage of pT1 and pT3 cancers. Renal sinus fat or vascular invasion was found to be present in 5 (13.9%) RCCs of ≤4 cm, 9 (19.1%) RCCs of >4 cm but ≤7 cm and 38 (64.4%) RCCs of >7 cm in maximum dimension. Perinephric fat was invaded in 11 (9.5%) RCCs of ≤4 cm, 15 (24.2%) RCCs of >4 cm but ≤7 cm and 21 (31.3%) RCCs of >7 cm. RCCs of >7 cm invaded renal sinus fat 11 times more often than tumors of <7 cm, while perinephric fat was invaded 5.6 times more often by RCCs of >7 cm than by smaller tumors.

Size 4.5 cm can be a predictive marker for renal sinus fat and perinephric fat invasion with the sensitvity of 80% and 90%, respectively. However, specificity of this marker is too low, on the level of 28% and 26.5%.

We found that 28 (77.8%) of RCC and 25 (80.6%) of ccRCC of ≤4 cm were limited to the kidney. This frequency gradually declined to 34 (72.3%) of RCC and 33 (73.3%) of ccRCC as tumor size increased to >4 cm but did not exceed 7 cm. However, percentage of tumors of >7 cm limited to the kidney decreased precipitously to 17 (28.8%) of RCC and 13 (25.0%) of ccRCC.

Extrarenal extension of renal carcinoma - renal sinus fat and perinephric fat invasion

A significant relationship existed between renal sinus fat and perinephric fat invasion for total

Table 1. Clinicopathologic characteristics

Histologic subtype of RCC [n (%)]	ccRCC 203 (81.53%)	pRCC t. 1 15 (6.02%)	pRCC t. 2 17 (6.83%)	chRCC 14 (5.62%)	Total RCC 249 (100%)
Age, years (mean ± SD)	63.24 ± 10.22	69.13 ± 9.47	64.12 ± 6.3	64.50 ± 8.74	63.73 ± 9.3
Gender [n (%)]					
Female	74 (36.45%)	5 (33.33%)	5 (29.41%)	9 (64.29%)	93 (37.35)
Male	129 (63.55)	10 (66.67%)	12 (70.59%)	5 (35.71%)	156 (62.65%)
Type of operation [n (%)]					
Radical nephrectomy	128 (63.05%)	4 (26.67%)	7 (41.18%)	3 (21.43%)	142 (57.03%)
Partial nephrectomy	75 (36.95%)	11 (73.33%)	10 (58.82%)	11 (78.57%)	107 (42.97%)
Tumor location [n (%)]					
Right kidney	111 (54.68%)	7 (53.33%)	12 (70.59%)	7 (50.00%)	137 (55.02%)
Left kidney	92 (45.32%)	8 (46.67%)	5 (29.41%)	7 (50.00%)	112 (44.98%)
Tumor size, cm (mean ± SD)	5.62 ± 3.30	5.48 ± 4.71	5.71 ± 3.97	4.19 ± 2.27	5.54 ± 3.39
Tumor stage [n (%)]					
pT1	119 (58.62%)	9 (60.00%)	9 (52.94%)	6 (42.86%)	143 (57.43%)
pT2	19 (9.36%)	3 (20.00%)	2 (11.76%)	2 (14.29%)	26 (10.44%)
pT3	64 (31.53%)	3 (20.00%)	6 (35.29%)	6 (42.86%)	79 (31.73%)
pT4	1 (0.49%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.40%)
WHO/ISUP grading[a]					
G1	78 (38.42%)	5 (33.33%)	2 (11.76%)		85 (36.17%)
G2	73 (35.96%)	8 (53.33%)	11 (64.71%)		92 (39.15%)
G3	25 (12.32%)	0 (0.00%)	1 (5.88%)		26 (11.06%)
G4	27 (13.30%)	2 (13.33%)	3 (17.65%)		32 (13.62%)
Tumor necrosis area % (mean ± SD)	8.25 ± 19.24	19.33 ± 34.48	11.24 ± 21.07	4.29 ± 13.42	8.90 ± 20.38
Sarcomatoid area % (mean ± SD)	1.23 ± 5.85	0.67 ± 2.58	5.35 ± 19.39	0.00	1.5 ± 7.54
Rhabdoid area % (mean ± SD)	0.65 ± 4.36	0.00 ± 0.00	0.00 ± 0.00	0.00	0.56 ± 4.05
Lymphatic invasion present [n (%)]	6 (2.96%)	0 (0.00%)	4 (23.53%)	0 (0.00%)	10 (4.02%)
Angioinvasion present [n (%)]	39 (19.21%)	0 (0.00%)	4 (23.53%)	1 (7.14%)	44 (17.67%)
Neuroinvasion present [n (%)]	2 (0.99%)	0 (0.00%)	2 (11.76%)	0 (0.00%)	4 (1.61%)
Renal fibrous capsule invasion present [n (%)]	115 (56.65%)	8 (53.33%)	11 (64.71%)	8 (57.14%)	142 (57.03%)
Perinephric fat invasion present [n (%)]	35 (17.24%)	2 (13.33%)	5 (29.41%)	4 (28.57%)	46 (18.47%)
Renal sinus fat invasion present [n (%)][b]	32 (25.00%)	0 (0.00%)	4 (57.14%)	1 (33.33%)	37 (26.06%)
Renal sinus vascular invasion present [n (%)][b]	30 (23.44%)	0 (0.00%)	4 (57.14%)	1 (33.33%)	35 (24.65%)

Legend: ccRCC - clear cell renal cell carcinoma, pRCC - papillary renal cell carcinoma, chRCC - chromophobe renal cell carcinoma. [a]rated only for ccRCC, pRCC and total RCC without chRCC. [b]rated only for cases treated by radical nephrectomy.

RCC, ccRCC and pRCC. If renal sinus fat infiltration was present, perinephric fat was invaded significantly more often. Results of our study showed that fat tissue was more often invaded through the renal sinus than through the renal capsule in case of total RCC and each morphotype. In our study perinephric fat invasion was an isolated finding in 16 (11.3%) RCCs - 15 (11.7%) ccRCCs and 1 (9.1%) pRCC. Isolated renal sinus fat infiltration was present in 20 (15.6%) RCCs - 18 (14.1%) ccRCCs, 1 (9.1%) pRCC and 1 (33.1%) chRCC. Perinephric fat invasion occurred in addition to renal sinus invasion in 17 (12.0%) RCCs - 14 (10.9%) ccRCCs and 3 (27.3%) pRCCs. Interestingly, renal sinus fat or vascular infiltration was found to be more common in ccRCC (22.2%) than in pRCC (15.6%) and chRCC (14.3%).

Renal sinus vascular infiltration and main renal vein invasion

RCC has a predilection for intravenous growth in the form of so-called tumor thrombus which was present in our study on gross examination in 15 (11.7%) and 18 (12.7%) of newly diagnosed patients with ccRCC and total RCC, respectively. Frequency of microscopic renal sinus vascular invasion is presented in **Table 1**. The main renal vein invasion was not significantly correlated with renal sinus fat and perinephric fat invasion. However, in cases of total

Table 2. WHO/ISUP nucleolar grading related to mean tumor size, pathologic stage of primary tumor (pT), lymph node involvement (pN+), mean tumor necrotic area, renal sinus fat (F+) and vascular (V+) invasion for total renal cell carcinoma

Grade	Tumor size [cm]	pT 1-2 [%]	pT 3-4 [%]	pN+ [%]	Necrotic area [%]	F+ [%]	V+ [%]
G1 (n=85)	3.69	42.31	21.62	5.26	1.58	5.56	29.25
G2 (n=92)	5.51	39.1	39.19	10.53	5.16	41.67	35.85
G3 (n=26)	7.79	10.9	12.16	5.26	17.12	13.89	19.81
G4 (n=32)	9.28	7.69	27.03	31.58	34.41	38.89	15.09
	R=0.541	P<0.001		P>0.5 (NS)	R=0.572	P<0.05	P<0.01
	P<0.0001				P<0.0001		

Legend: NS - non-significant results.

Table 3. WHO/ISUP nucleolar grading related to mean tumor size, pathologic stage of primary tumor (pT), lymph node involvement (pN+), mean tumor necrotic area, renal sinus fat (F+) and vascular (V+) invasion for clear cell renal cell carcinoma

Grade	Tumor size [cm]	pT 1-2 [%]	pT 3-4 [%]	pN+ [%]	Necrotic area [%]	F+ [%]	V+ [%]
G1 (n=78)	3.66	45.86	21.54	0	1.4	6.25	3.45
G2 (n=73)	5.9	34.59	38.46	33.33	4.37	43.75	41.38
G3 (n=25)	7.86	12.03	13.85	16.67	17.6	15.63	13.79
G4 (n=27)	8.44	7.52	26.15	50	29.85	34.38	41.38
	R=0.556	P<0.001		P>0.5 (NS)	R=0.610	P<0.01	P<0.001
	P<0.0001				P<0.0001		

Legend: ns - non-significant results.

RCC and ccRCC with perinephric fat invasion, renal sinus vascular invasion could be expected with a higher probability.

Pathologic stage of lymph node metastases (pN)

Regional lymph node dissection was performed in 20 of surgeries for renal cancer (14 ccRCCs, 5 pRCCs and 1 chRCC). Among them 10 (50.0%) cases had lymph node metastases - 6 ccRCCs and 4 pRCCs.

Necrosis: pRCC was shown to more frequently contain necrotic areas (40.0% of type 1 and 41.2% of type 2) than either ccRCC (26.6% of cases) or chRCC (14.3%). The percentage of tumor necrotic area representing the tumor is presented in **Table 1**. We observed a positive correlation between an area of tumor necrosis and pT stage, size of renal cancer, its grade, and a proportion of sarcomatoid and rhabdoid component. The above correlation held for total RCC, ccRCC and pRCC.

Nucleolar grading: Nucleolar grading was significantly higher in total RCC and ccRCC with lymphovascular invasion, fibrous renal capsule/perinephric fat/renal sinus fat, and vascular infiltration. Additionally, nucleolar grade was significantly related to the pT stage, mean tumor size, and mean percentage of necrotic area within the tumor. **Tables 2** and **3** summarize the relation between the different data and nucleolar grading.

Sarcomatoid and rhabdoid differentiation: In our series sarcomatoid element was seen in 21 (8.4%) RCCs - 17 (8.4%) ccRCCs and 4 (12.5%) pRCCs. Total RCC displayed rhabdoid change in 8 (3.2%) tumors; all cases concerned ccRCC. The proportion of sarcomatoid and rhabdoid area representing the tumor is presented in **Table 1**. Microscopically, all neoplasms with sarcomatoid or rhabdoid differentiation were biphasic, with both carcinomatous and sarcomatoid or rhabdoid components. Rhabdoid foci were seen only in 2 (<1.0%) RCCs (both ccRCCs) with sarcomatoid change. We observed a correlation, especially for ccRCC, between sarcomatoid/rhabdoid transformation and size of the tumor, pT stage, perinephric fat infiltration, and renal sinus fat invasion.

Discussion

We present an over 4-year study of histologic findings in 249 RCCs. It is one of the few such studies with almost 50% patients treated by nephron-sparing surgery (NSS). Thus almost half of the tumors were localized and ≤4 cm, which undoubtedly influenced the results of our study. Moreover, due to the increasing number of indications for NSS and increasing number of RCC tumors detected as a result of the widespread use of radiological techniques who are candidates for partial nephrectomy, clinicopathologic characteristics of patients with renal cancer will be able to be similar to ours.

In the 8th edition of AJCC, tumor limited to the kidney and measuring >7 cm is classified as pT2, but likelihood of extrarenal extension, especially renal sinus invasion, increases with tumor size, so that true pT2 RCC is very rare [11, 12]. Similarly we observed pT2 RCC much less often than pT1 and pT3 tumors. Taneja et al. [11] reported tumor size >5 cm as the indicator of high likelihood of renal sinus invasion, but they did not report the sensitivity and specificity of this value. We demonstrated size 4.5 cm as a predictive marker for renal sinus fat and perinephric fat invasion with high sensitivity, but low specificity. Thus, renal sinus and perinephric fat should be carefully investigated particularly for tumors greater than 4-5 cm in size. Bonsib et al. [13] showed that only 32% of ccRCC of >4 cm were confined to the kidney, and this decreased to 3% for tumors of >7 cm. However, other RCC types, such as pRCC and chRCC, are more likely to reach a larger size without renal sinus invasion [11, 13]. Our own experience showed decreasing percentage of total RCC and ccRCC limited to the kidney with increasing tumor size. However, the proportion of tumors >7 cm confined to the kidney was higher than in the cited research. Unfortunately, the number of pRCC and chRCC in our data are not large enough to generalize this conclusion for these morphotypes.

Bonsib et al. [13] found that renal sinus invasion is a key invasive pathway, especially for ccRCC. The reason is lack of a fibrous barrier to delineate the renal sinus from the parenchyma, whereas the perinephric fat tissue and renal parenchyma are separated by fibrous capsule. Therefore, theoretically, renal sinus invasion is more likely to occur than perinephric fat infiltration [14]. On the other hand Kirkali et al. [15] reported that the fat tissue was usually invaded through the renal capsule. This former observation is in line with ours - we observed that renal sinus fat was invaded more often than perinephric fat as regards each histologic subtype of renal cancer and total RCC. It should be indicated that the invasion of the perinephric fat was evaluated for a total of 249 tumors, while infiltration of the renal sinus only for cases treated by radical nephrectomy (142 cancers), because cases treated by NSS did not contain renal sinus tissue.

In the literature, for ccRCC, perinephric fat invasion alone is uncommon in the absence of vein branch or renal sinus invasion [16]. In our research the frequency of isolated perinephric fat invasion (11.7%) was comparable with frequency of coincident infiltration of perinephric fat and renal sinus (10.9%) for ccRCC. Interestingly, if renal sinus fat infiltration was present, perinephric fat was invaded significantly more often.

According to the scientific literature, intravenous tumor growth is present in 4-10% of newly diagnosed patients with renal cancer [11]. Our experience showed that it was present slightly more often, in 12.7% of RCCs.

Lymph node dissection is performed in <5% of surgeries for renal cancer [12]. Taneja & Williamson [11] reported that 7-17% of RCC tumors have hilar or locoregional lymph node metastases. In current practice lymph node dissection is considered unnecessary in patients with clinically negative lymph nodes [11]. Among our cases, lymph node dissection was performed in 8% of surgeries. Lymph node metastases were present in up to 50% of cases. This high percent of patients with positive lymph nodes is most likely associated with the fact that these lymph nodes were clinically positive and therefore it was decided to remove them.

In the literature, pRCC has been shown to more frequently contain necrotic areas (39-52%) than either ccRCC (31-40%) or chRCC (39-52%) [17]. This tendency was similar in our study; however we observed a lower frequency of tumor necrosis in cases of ccRCC (26.6%) and chRCC (14.3%). There was no difference in frequency of tumor necrosis between type 1

(40.0%) and type 2 (41.2%) pRCC in our research group. Additionally, we assessed the percentage of tumor area occupied by necrosis. Interestingly pRCC demonstrated the largest area of tumor necrosis (32.0%) compared to ccRCC (19.2%) and chRCC (13.4%). Similar to other reports [18-20], we revealed that an increased area of tumor necrosis means a higher pT stage, higher grade, and higher proportion of sarcomatoid component. Furthermore, those reports showed a positive correlation between tumor necrosis and lymph node invasion (which was not confirmed by us), angioinvasion, and distant metastasis.

Our experience demonstrated that nuclear grading was significantly related to the pT stage, mean tumor size, mean necrotic area, renal sinus fat, and vascular invasion. It is in line with observation of Ficarra et al. [21].

The limitation of our research was an inability to obtain information about clinical outcomes (relapse, metastasis, overall and progression free survival) and correlate them with histologic features assessed in our study.

In conclusion, we demonstrated that tumor size represents one of the most important factors determining biological behavior of RCC. It should be emphasized that renal sinus and perinephric fat should be carefully investigated, particularly in case of tumors greater than 4-5 cm. Furthermore, if infiltration of the renal sinus is present, perinephric fat is invaded significantly more often. Currently, NSS has become the standard of care for small renal masses; there is an increasing acceptance for partial nephrectomy in larger tumors, even >7 cm. However, only 28.8% of RCC of >7 cm is limited to the kidney and these tumors invade renal sinus fat 11 times more often and perinephric fat 5.6 times more often than smaller cancers. All these facts should be taken into account during the decision-making process by the urologists and oncologists dealing with RCC to optimize the treatment.

Disclosure of conflict of interest

None.

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