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Review Articles

Chromosomal numerical aberration pattern in papillary renal cell carcinoma: Review article☆

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ABSTRACT

Traditionally, papillary renal cell carcinomas (PRCCs) have been divided in two subgroups – type 1 and type 2. Based on recent molecular and genetic developments in the understanding of RCCs, it seems that this traditional classification may not be adequate and that the spectrum of PRCCs is much wider than initially proposed. Small series of distinct types of PRCC which do not fit into the above mentioned categories have been described in the literature. Published studies investigating molecular genetic changes in various types of PRCCs have shown that the molecular genetic features are remarkably heterogeneous across the whole spectrum of PRCCs. Of all PRCC subtypes/variants, PRCC type 1 seems to be a genetically uniform group, while other types showed different degrees of heterogeneity. Among different molecular-genetic features, chromosomal numerical aberration status is one of the most frequently studied features so far. It is becoming more evident that tumor type-specific chromosomal numerical aberration status in PRCCs may not exist. In this review, we present the most current knowledge concerning chromosomal numerical aberration status in PRCCs.

1. Introduction

Papillary renal cell carcinoma (PRCC) is the second most common type of renal cell carcinoma (RCC) [1]. Historically, PRCCs have been divided in two subgroups (based on morphological and immunohistochemical features) – type 1 and type 2 [2,3]. However, we now know that PRCCs were composed of a heterogeneous group of RCCs including translocation RCCs, hereditary leiomyomatosis associated RCCs, and other mixed and unclassified PRCCs. Based on recent molecular and genetic developments in the understanding of RCCs, it is evident that the traditional PRCC type 1/type 2 classification may not be adequate and that the spectrum of PRCCs is much wider than initially proposed. In fact, on daily surgical pathology practice, it is not uncommon to encounter tumors with overlapping (mixed) histology or even distinct subtypes of PRCC which do not fit into the above-mentioned categories.

In 1997 Kovacs et al. published "The Heidelberg classification of renal cell tumors", which was the first classification integrating molecular genetic features as one of the diagnostic tools applicable to renal cell tumors [4]. In recent years, there have been many studies examining and describing molecular genetic changes in PRCCs. All these studies have shown that the molecular genetic changes are remarkably heterogeneous across the whole spectrum of PRCCs and that molecular-genetic analysis cannot be used as a universal diagnostic tool in this regard.

In this review, we presented the most current knowledge concerning chromosomal numerical aberration pattern (CNAP) as one of the aspects of molecular-genetic backgrounds in PRCCs.

2. PRCC type 1

Traditionally, PRCCs type 1 are composed of neoplastic cells with scant cytoplasm and low-grade nuclei (according to Fuhrman grading system/ISUP) arranged in a single layer (Fig. 1) [3].

Molecular genetic changes in PRCCs type 1 are most uniform among all subtypes of PRCCs. Gains and losses of chromosomes in PRCCs type 1, described in different studies, are summarized in Tables 1 and 2.

Historically, the gains of chromosomes 7 and 17, which are believed to be the most common and characteristic CNAP among the entire spectrum of PRCCs, are most typically seen in PRCC type 1. Other frequently encountered chromosomal gains in PRCCs type 1 are the gains of chromosomes 3, 12, 16, and 20. There are also some studies

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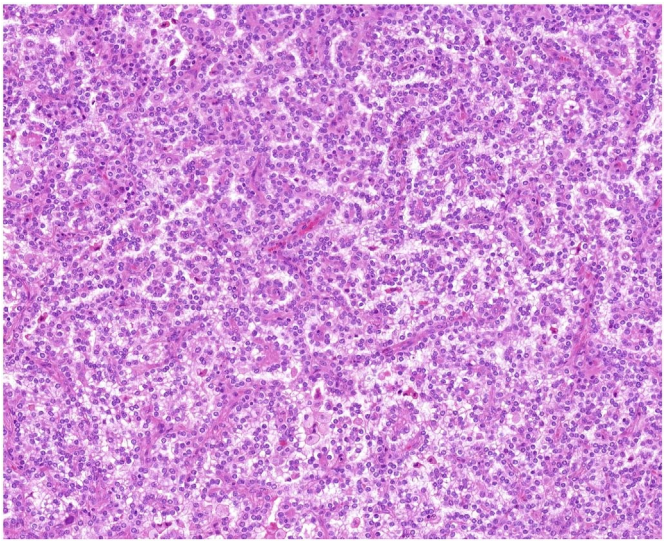

Fig. 1. Papillary renal cell carcinomas type 1 are composed of neoplastic cells with scant cytoplasm and low-grade nuclei arranged in papillary or tubulopapillary pattern.

which have demonstrated the gains of chromosomes 2, 4, 5, 6, 8, 13, and 18 only in a small proportion of cases. (Table 1).

The loss of chromosome Y in male patients is another typical chromosomal aberration pattern observed in PRCC type 1. There are also individual cases showing losses of various chromosomes including 1, 2, 4, 5, 7, 8, 9, 10, 11, 14, 15, 16, 18, 19, 20, 21, and 22 [5-10] (Table 2).

3. PRCC type 2

By definition, PRCC type 2 histologically presents with neoplastic cells with abundant eosinophilic cytoplasm, high-grade nuclear features (according to Fuhrman grading system/ISUP) and nuclear pseudostratification (Fig. 2) [3].

CNAP in PRCC type 2 has not proven to be as constant as seen in PRCC type 1. It is worth noting that although the gains of chromosomes 7 and 17 are most commonly referred within the literature for PRCC type 2, these changes in fact are only found in a smaller percentage of cases. A large number of different chromosomal aberrations have been described in PRCC type 2, but there is a large variability in their occurrence and frequencies in different studies. Nonetheless, the relatively more frequent chromosomal aberrations in PRCCs type 2 are the gains of chromosomes 12, 16 and 20. Of note, other chromosomal gains described with enormous variability in a small percentage of the cases include gains of chromosomes 1, 2, 3, 4, 5, 6, 8, 9, 13, 18, 19 and 22 [5-10] (Table 3).

The loss of chromosome Y in male patients has been reported in PRCC type 2 in different studies. There are also sporadic cases showing losses of different chromosomes and their parts including 1, 2, 3, 4,5, 6, 7, 8, 9, 10, 12, 13, 14, 15, 17, 18, 19, 20, 21, 22, and X [5-10] (Table 4).

4. Oncocytic PRCC

Oncocytic PRCCs (OPRCC) are tumors with papillary architecture, with papillae being covered by single layer of neoplastic cells showing abundant and granular deeply eosinophilic cytoplasm (oncocytic cells) (Fig. 3). Although papillary growth pattern is a constant feature, solid areas may also be seen infrequently. Ultrastructurally, the cytoplasm is packed with numerous mitochondria [11]. These tumors usually show a relatively indolent clinical behavior [11,12], although some tumors can behave aggressively [13,14].

CNAP is not uniform in this poorly understood subtype of PRCC. The gains of chromosomes 7 and 17 are the most common chromosomal aberrations reported by different studies. There are also some studies describing even the gains of chromosomes 3 and 11. Loss of chromosome Y in male patient is occasionally seen in OPRCC. Other described numerical aberrations are the losses of chromosomes 1, 4, 14 as wells as

Table 1
PRCC type 1 - gains of chromosomes.

	1+	2+			3+		4+	5+	6+	7+				8+	9+	12+			13+	16+			17+			18+	19+	20+		21+		22+
	1q+	2+	2p+	2q+	3+	3q+	4+	5+	6+	7+	7p+	7q+	7+,17+	8+	9+	12+	12p+	12q+	13+	16+	16p+	16q+	17+	17p+	17q+	18+	19q+	20+	20q+	21+	21q+	
Jiang et al. [5] CGH											9/9 100%	6/9 66.7%						2/9 22.2%				5/9 55.6%		9/9 100%	9/9 100%				5/9 55.6%			
Kovac et al. [6] Sequence analysis		1/6 16.7%			1/6 16.7%					4/6 66.7%			3/6 50%			3/6 50%				2/6 33.3%			4/6 66.7%								
Yu et al. [7] FISH										20/30 66.7%													26/30 86.7%								
Marsaud et al. [8] aCGH + Karyotyping + FISH		1/15 6.7%			4/15 26.7%			2/15 13.3%	1/15 6.7%	15/15 100%			15/15 100%	1/15 6.7%		6/15 40%			2/15 13.3%	8/15 53.3%			15/15 100%					6/15 40%			1/15 6.7%	2/15 13.3%
Gunaw et al. [9] Cytogenetic analysis		4/34 11.8%			7/34 20.6%			4/34 11.8%	1/34 2.9%	30/34 88.2%			28/34 82.4%	4/34 11.8%		12/34 35.3%			4/34 11.8%	22/34 64.7%			32/34 94.1%			1/34 2.9%		15/34 44.1%				
Antonelli et al. [10] Karyotyping		1/13 7.7%			4/13 30.8%		1/13 7.7%			9/13 69.2%			9/13 69.2%			5/13 38.5 %			1/13 7.7%	4/13 30.8%			11/13 84.6%					4/13 30.8%				

Table 2
PRCC type 1 - chromosomal losses.

	1-	2-	3-		4-		5-	6-		7-	8-	9-			10-	11-		13	14-	15-	16-		17-	18-		19-	20-	21-		22-		X-			Y-
	1p-	2-	3-	3q-	4-	4q-	5-	6p-	6q-	7-	8-	9-	9p-	9q-	10-	11-	11q-	13q-	14-	15-	16-	16p-	17-	18-	18q-	19-	20-	21-	21q-	22-	22q-	X-	Xp-	Xq-	Y-
Jiang et al. [5] CGH	3/9 33.3%					5/9 55.6%			4/9 44.4%					4/9 44.4%				6/9 66.7%															2/9 22.2%	3/9 33.3%	
Kovac et al. [6] Sequence analysis	1/6 16.7%																							1/6 16.7%		1/6 16.7%		1/6 16.7%		2/6 33.3%					
Yu et al. [7] FISH											0/30					2/30 6.7%								6/30 20%										18/20M 90%
Marsaud et al. [8] aCGH + Karyotyping + FISH	1/15 6.7%				1/15 6.7%							1/15 6.7%	1/15 6.7%						1/15 6.7%	1/15 6.7%		1/15 6.7%						1/15 6.7%		1/15 6.7%				9/9M 100%
Gunawan et al. [9] Cytogenetic analysis		1/34 2.9%					3/34 8.8%			1/34 2.9%	1/34 2.9%	3/34 8.8%			1/34 2.9%	1/34 2.9%			3/34 8.8%		1/34 2.9%			3/34 8.8%			1/34 2.9%	2/34 5.9%		4/34 11.8%		1/34 2.9%			24/28M 85.7%
Antonelli et al. [10] Karyotyping												1/13 7.7%							1/13 7.7%				1/13 7.7%					1/13 7.7%			1/13 7.7%			7/9M 77.8%

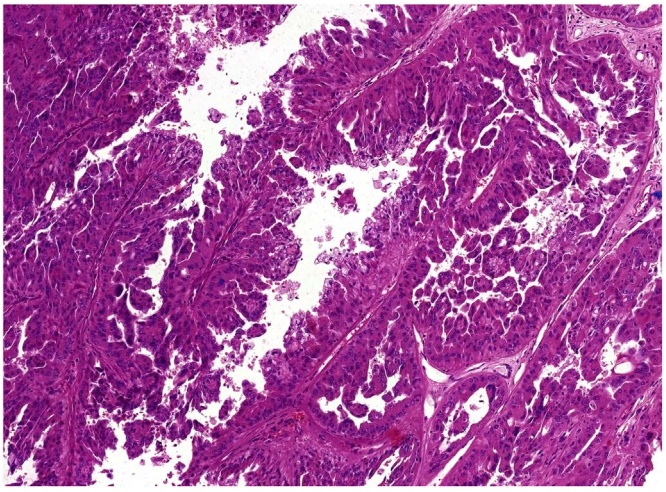

Fig. 2. Papillary renal cell carcinoma type 2 is characterized by papillary growth pattern and neoplastic cells with pseudostratification, eosinophilic cytoplasm with high-grade nuclei.

loss of gonosome X [11-13,15-17]. (Table 5).

The largest study to date investigating CNAP in OPRCC showed interesting results. A substantial proportion of OPRCCs in this study showed disomic status of chromosomes 7 and 17, some with deletion of chromosome 14, deletion of 1p (locus 1p36) and some cases had loss of chromosomes Y. Interestingly, all such patterns are also well-known to be characteristic for renal oncocytoma (RO). The authors reported that approximately one third of cases showed the gains of chromosomes 7 and/or 17. There were a small proportion of tumors demonstrating loss of chromosome Y in male patients, which is one of the chromosomal patterns traditionally believed to be characteristic for PRCC. Some cases (7/24) showed none or variable and nonspecific chromosomal abnormalities (i.e., loss of chromosome 17, gonosome X) [14] (Table 5).

5. Other variants/subtypes of PRCCs

In addition to the most common and well-described variants of PRCCs, a number of small series of other different types of PRCCs have been also described, which interestingly showed variable numerical aberration patterns.

"Mucin"-secreting PRCC has been described in different studies. These tumors have papillary architecture with some cases demonstrating tubulopapillary or solid growth patterns, and producing variable amount of mucin-like material intra- or/and extracellularly (Fig. 4) [18-20]. A recent molecular-genetic study by our group demonstrated the gains of chromosomes 7 (2/4 cases), 17 (3/4 cases), 16 (1/2 cases) and loss of chromosome Y in all male cases (Table 6) [20].

Cystic and necrotic PRCC is an unusual variant of PRCC type 1. These tumors usually present as huge renal cystic lesions filled with large amount of necrotic (liquefactive necrosis) and hemorrhagic contents. The cystic spaces are lined by a very limited amount of viable neoplastic tumor cells, creating potential diagnostic challenges. These tumors are well encapsulated by fibroleiomyomatous stroma, which is

Table 3
PRCC type 2 - Gains of chromosomes.

		Jiang et al. [5] CGH	Kovac et al. [6] Sequence analysis	Yu et al. [7] FISH	Marsaud et al. [8] aCGH + Karyotyping + FISH	Gunawan et al. [9] Cytogenetic analysis	Antonelli et al. [10] Karyotyping
Y+	Y+				1/16 6.3%		
X+	Xq+				1/16 6.3%		
	X+				2/16 12.5%		
22+	22+					1/13 7.7%	
21+	21q+		1/20 5%		21+ 1/16 6.3%		
20+	20q+	4/16 25%			2/16 12.5%		
	20p+				1/16 6.3%		
	20+		2/20 10%		4/16 25%	8/13 61.5%	4/13 30.8%
19+	19q+		1/20 5%		1/16 6.3%		
	19p+				1/16 6.3%		
	19+					2/13 15.4%	
18+	18p+		1/20 5%				
	18+					1/13 7.7%	1/13 7.7%
17+	17q+	11/16 68.8%	3/20 15%		3/16 18.8%		
	17p+	6/16 37.5%					
	17+		10/20 50%	15/26 57.7%	8/16 50%	7/13 53.9%	7/13 53.8%
16+	16q+	3/16 18.8%	1/20 5%		1/16 6.3%		
	16p+		1/20 5%		1/16 6,3%		
	16+		11/20 55%		4/16 25%	10/13 76.9%	7/13 53.8%
15+	15+				1/16 6.3%		
13+	13q+		1/20 50%		1/16 6.3%		
	13+				1/16 6.3%	3/13 23.1%	2/13 15.4%
12+	12q+	5/16 31.2%			1/16 6.3%		
	12p+		1/20 5%				
	12+		5/20 25%		9/16 56.3%	5/13 38.5%	4/13 30.8%
11+							1/13 7.7%
10+	10p+				1/16 6.3%		
	10+				1/16 6.3%	1/13 7.7%	1/13 7.7%
9+	9+		1/20 5%				
8+	8q+				1/16 6.3%		
	8+		2/20 10%		6/16 37.5%	2/13 15.4%	
7+	7+,17+		8/20 40%		5/16 31.3%	5/13 38.5%	6/13 46.2%
	7q+	5/16 31.2%					
	7p+	5/16 31.2%					
	7+		9/20 45%	16/26 61.5%	8/16 50%	9/13 69.2%	8/13 61.5%
6+	6p+		1/20 5%		1/16 6.3%		
	6+						1/13 7.7%
5+	5q+				3/16 18.8%		
	5+		1/20 5%		3/16 18.8%	1/13 7.7%	1/13 7.7%
4+	4+				1/16 6.3%	1/13 7.7%	
3+	3q+		1/20 5%		3/16 18.8%		
	3+		1/20 5%		1/16 6.3%	5/13 38.5%	
2+	2q+		2/20 10%				
	2p+						
	2+		1/20 5%		2/16 12.5%	3/13 23.1%	
1+	1q+		2/20 10%		1/16 6.3%		
	1p+				1/16 6.3%		

Table 4
PRCC type 2 - chromosomal losses.

		Jiang et al. [5] CGH	Kovac et al. [6] Sequence analysis	Yu et al. [7] FISH	Marsaud et al. [8] aCGH + Karyotyping + FISH	Gunawan et al. [9] Cytogenetic analysis	Antonelli et al. [10] Karyotyping
Y-	Y-			8/12M 66.7%	7/11M 63.6%	9/10M 90%	7/10M 70%
X-	Xq-	6/16 37.5%					
	Xp-	5/16 31.2%			1/16 6.3%		
	X-		4/20 20%		3/16 18.8%		2/13 15.4%
22-	22q-		1/20 5%				
	22-		2/20 10%		2/16 12.5%	4/13 30.8%	1/13 7.7%
21-	21q-		1/20 5%				
	21-				5/16 31.3%	2/13 15.4%	1/13 7.7%
20-	20q-				1/16 6,3%		
	20p-		1/20 5%				
	20-					1/13 7.7%	2/13 15.4%
19-	19-				1/16 6.3%	1/13 7.7%	
18-	18q-		1/20 5%		2/16 12.5%		
	18-		2/20 10%	13/26 50%	2/16 12.5%	6/13 46.2%	1/13 7.7%
17-	17p-		1/20 5%				
	17-					3/13 23,1%	1/13 7.7%
16-	16q-				3/16 18.8%		
	16p-				1/16 6.3%		
	16-					1/13 7.7%	
15-	15-				3/16 18.8%	3/13 23,1%	2/13 15.4%
14-	14q-		1/20 5%				
	14-		1/20 5%		8/16 50%	3/13 23,1%	3/13 23.1%
13-	13q-	3/16 18.8%					
	13-				1/16 6.3%	2/13 15.4%	1/13 7.7%
11-	11q-				2/16 12.5%		
	11-		1/20 5%	9/26 34.6%	3/16 18.8%	3/13 23,1%	1/13 7.7%
12-	12-					2/13 15.4%	
10-	10-				1/16 6.3%	2/13 15.4%	3/13 23.1%
9-	9q-	6/16 37.5%					
	9p-		1/20 5%		2/16 12.5%		
	9-		3/20 15%		2/16 12.5%	3/13 23,1%	2/13 15.4%
8-	8p-				1/16 6.3%		
	8-			6/26 23.1%	2/16 12.5%	3/13 23,1%	1/13 7.7%
7-	7q-		1/20 5%		1/16 6.3%		
	7-					1/13 7.7%	
6-	6q-	6/16 37.5%			1/16 6.3%		
	6p-		1/20 5%				
	6-				2/16 12.5%	1/13 7.7%	
5-	5-					2/13 15,4%	3/13 23.1%
4-	4q-	5/16 31.2%	1/20 5%				
	4-				1/16 6.3%	2/13 15.4%	1/13 7.7%
3-	3q-		1/20 5%				
	3p-		4/20 20%		5/16 31.3%		
	3-					1/13 7.7%	1/13 7.7%
2-	2q-		2/20 10%				
	2p-		2/20 10%				
	2-					3/13 23,1%	1/13 7.7%
1-	1q-				2/16 12.5%		
	1p-	4/16 25%	1/20 5%		2/16 12.5%		
	1-				3/16 18.8%	2/13 15.4%	2/13 15.4%

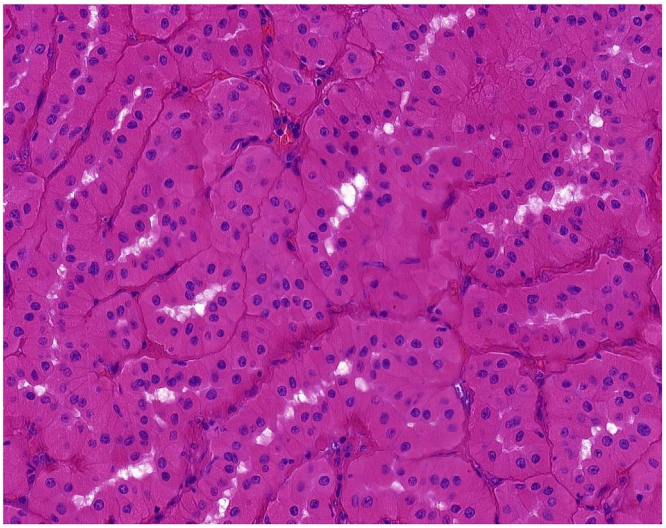

Fig. 3. So-called oncocytic papillary renal cell carcinoma is a poorly understood variant, composed of eosinophilic cells resembling in many aspects those in renal oncocytoma.

histologically indistinguishable from inflammatory pseudotumor. All such tumors were morphologically consistent with the diagnosis of PRCC type 1 and had non-aggressive behavior despite the presence of liquefactive necrosis. A molecular-genetic analysis of 10 cases by Peckova et al. showed non-homogenous changes including 5/8 analyzable cases with polysomy of chromosomes 7 and 17, and 5/7 analyzable male cases with loss of chromosome Y. No molecular-genetic abnormalities were detected in the remaining two cases (Table 7) [21].

Solid PRCC was originally described by Renshaw et al. in 1997 [22]. This type of PRCC is typically composed of tightly packed small compressed tubules (Fig. 5) and short abortive papillae with or without sparse true papillae. The neoplastic cells are monomorphic with scant cytoplasm and small nuclei [23]. Molecular genetic studies showed the gains of chromosomes 7 and 17 and loss of gonosome Y in male patients in high percentage of cases (Table 8) [22,24,25].

Warthin-like PRCC is another subtype of PRCC, which has considerable morphological resemblance to oncocytic PRCC. Warthin-like PRCC has predominant papillary architecture, with oncocytic neoplastic cells admixed with dense lymphoid stroma and tumor infiltrating lymphocytes (Fig. 6). Molecular genetic analysis performed on these tumors showed a wide heterogeneous spectrum of chromosomal changes (not even constant in this subgroup). In some cases no chromosomal changes were detected, while other cases showed the gains of chromosomes 1, 2, 5, 7, 8, 12, 17 and 21, with some cases demonstrated loses of chromosomes 1, 3, 14, 15, 18, 22 and Y [26] (Table 9).

PRCCs with clear cells are tumors with papillary architecture and clear cell morphology (Fig. 7). Some studies have suggested that the clear cell features may be associated with degenerative changes, hemorrhage and/or necrosis [27,28]. There are a number of studies which described such tumors and strictly followed results of molecular genetic analysis in further classifying these neoplasms. Fuzesi et al. reported loss of terminal 3p segment and loss of chromosome 14 in all such cases and further showed other chromosomal changes detected in individual cases. In another study, Salama et al. showed LOH 3p in 6/6 cases, and loss of chromosomes 7 and 17 in 4/6 and 6/6 cases, respectively. It should be noted that tumors examined in these two studies were rather evaluated from clear cell renal cell carcinoma (CCRCC) molecular genetic perspectives than PRCC. Further, the authors did not perform immunohistochemical studies in these cases [29,30]. On the other hand, Gobbo et al. performed immunohistochemical and cytogenetical analysis of 14 cases of RCC with papillary architecture and variable proportion of neoplastic cells with clear cytoplasm. According to their combined immunohistochemical and cytogenetical analysis, 9/14 cases were classified as PRCC, because of AMACR positivity, CK7 reactivity (in most cases), polysomy of chromosomes 7 or 17 and loss of chromosome Y in male cases [27]. Haudebourg et al. studied three RCC cases with the above-mentioned morphology and found polysomy of chromosomes 7 and 17 in 2/3 case (these were classified as PRCCs) and detected polysomy of 7 and 17, loss of gonosome Y concurrently with loss of heterozygosity (LOH) for chromosome 3 in 1/3 cases (this case was classified as hybrid tumor composed of PRCC and CCRCC). All tumors were positive for AMACR and CD10 (3/3), and 2/3 were immunoreactive for CK7 [31] (Table 10).

Biphasic squamoid alveolar RCC (BSARCC) was recently described as a distinct morphologic variant of PRCC. These tumors are composed of a distinctly dual cell populations including low-grade uniform small neoplastic cells with scant cytoplasm and round (or slightly elongated) nuclei and larger squamoid cells containing voluminous pink cytoplasm and large nuclei with prominent nucleoli (Fig. 8). Emperipolesis associated with squamoid cells is constant finding in all described cases [32,33]. Hes et al. showed the gains of chromosomes 7 and 17 in all analyzable cases (11/21) and loss of chromosome Y in 4/5 male cases. Table 11 presents other chromosomal abnormalities described in some cases included in this study [32]. On the other hand, Petersson et al. showed in their one suitable case for molecular-genetic analysis absolutely distinct results [34]. However, this case was later reclassified as unclassified RCC [32]. BSARCCs can be multifocal and also associated with other subtypes of RCC [33,35]. Further, these tumors can occur in a familial context of hereditary PRCC associated with *MET* mutation [36]. This rare morphologic variant of PRCC has also been described in kidney allografts [37].

6. Discussion

The classification of renal neoplasms has dramatically changed in recent years. Although histology and immunohistochemical assays still serve as the main diagnostic drivers, in the era of precision medicine, molecular genetic analysis plays an integral role in diagnostically challenging cases as well as enhancing the classification of renal tumors based on molecular biomarkers.

The traditional general opinion concerning chromosomal numerical aberration status in PRCC includes a combination of gains of chromosomes 7 and 17 with loss of chromosome Y in male patients. One of the challenges in verifying such claim comes with the fact that it would be nearly impossible to distinguish various histologic subtypes of PRCCs used in earlier studies along with employing small number of cases.

From historical perspective, some of “PRCCs” are now recognized as completely different tumors and distinct entities. For instance, translocation PRCC (Xp11.2) was recognized as a separate neoplastic entity in the WHO 2004 classification [38]. RCC associated with hereditary leiomyomatosis (HLRCC) was considered as a hereditary counterpart of PRCC type 2 in the WHO 2004 and was subsequently recognized as a separate entity in the Vancouver ISUP classification. Clear cell papillary RCC (CCPRCC) is another example of such, which was introduced as a new entity by the Vancouver ISUP classification [39]. Both of these neoplasms (HLRCC and CCPRCC) were later adopted by the WHO 2016

Table 5
Oncocytic PRCC – chromosomal gains and losses.

		2+	3+		5+	7+	11+	16+	17+		7+,17+ in common	1-		4-	14-	15-	17-	Y-	X-
		2+	3+	3p+	5+	7+	11q+	16+	17+	17q+	7+,17+	1-	1p-	4q-	14-	15-	17-	Y-	X-
Xia et al. [15]	FISH					3/5 60%			2/5 40%		1/5							1/4 M 25%	
Hes et al. [11]	FISH					7/12 58.3%			8/12 66.7%		5/12 41.7%							3/10M 30%	
Park et al. [13]	Array CGH			3/4 75%			2/4 50%			2/4 50%				1/4 25%					
Lefevre et al. [12]	Karyotyping + CGH	1/5 20%	1/5 20%		1/5 20%			1/5 20%				2/5 40%			3/5 60%	2/5 40%		3/5 M 60%	
Han et al. [16]	FISH					7/14 50%			6/14 42.9%									2/8M 25%	
Kunju et al. [17]	FISH					6/6 100%			6/6 100%		6/6 100%							2/4M 50%	
Michalova et al. [14]	FISH					5/22 22.7%			6/22 27.3%		4/22 18.2%		6/21 28.6%		3/22 13.6%		5/22 22.7%	8/13M 61.3%	2/23 8.7%

classification [1].

The most recent WHO 2016 classification of renal tumors still recognizes the traditional subtyping of PRCC into type 1 and type 2. Oncocytic PRCC is currently mentioned as a provisional entity in the recent WHO 2016, which can be possibly recognized as PRCC type 3. The current WHO classification also recognizes the fact that there are renal tumors with mixed histology which may not fit into any of these categories [1].

During the last 15 years, many subtypes and variants of PRCC have been described, which do not fit in any of the officially recognized WHO tumor categories (i.e., type 1, type 2, possibly oncocytic). There are a number of studies describing small series of morphologically distinct PRCCs such as Warthin-like PRCC [26], solid PRCC [22-25], mucinous PRCC [18-20], biphasic squamoid alveolar RCC [32-36], and PRCC with clear cells [27,29,30,40].

It is evident that PRCCs are composed of a diverse and heterogeneous group of tumors with distinct subgroups of papillary or tubulopapillary architecture. These tumors can show different histological and even immunohistochemical profiles. From histologic point of view, these tumors can present in a wide range of morphological features such as small basophilic cells with scant cytoplasm, cells with abundant eosinophilic cytoplasm (oncocytic), larger basophilic cells with squamoid feature and emperipolesis or even cells with clear cytoplasm. In addition to typical papillary and tubulopapillary architecture, PRCC can present with predominant solid feature, as well as biphasic architecture with solid islands surrounded by alveolar-like structures. PRCCs can produce large necrotic and cystic changes or demonstrate mucin-like production. It is apparent that all such variations in PRCCs can create potential diagnostic challenges.

Imumnohistochemicaly, PRCCs express several different antibodies. Traditionally, vimentin, AMACR and CK7 were considered characteristic. PRCCs are almost constantly positive for vimentin and AMACR, however they show variable reactivity for CK7 [1]. Positivity of CK7 is more common in type 1 PRCC, while it is more variable in PRCC type 2 (some studies reported CK7 positivity in about 50% of PRCCs type 2) [41].

The above-mentioned subtypes/variants of PRCCs are shown to have diverse chromosomal numerical aberration patterns. PRCC type 1 has the most uniform molecular genetic changes across the whole spectrum of PRCCs. Polysomy of chromosomes 7 and 17 are very

Table 6
"Mucin" secreting PRCC – chromosomal gains and losses.

		7+	17+	7+,17+ in common	16+	Y-
Pivovarcikova et al. [20]	ACGH	1/1 100%	1/1 100%	1/1 100%	1/1 100%	1/1 100%
	FISH	2/4 50%	3/4 75%	1/4 25%	1/2 50%	4/4 100%

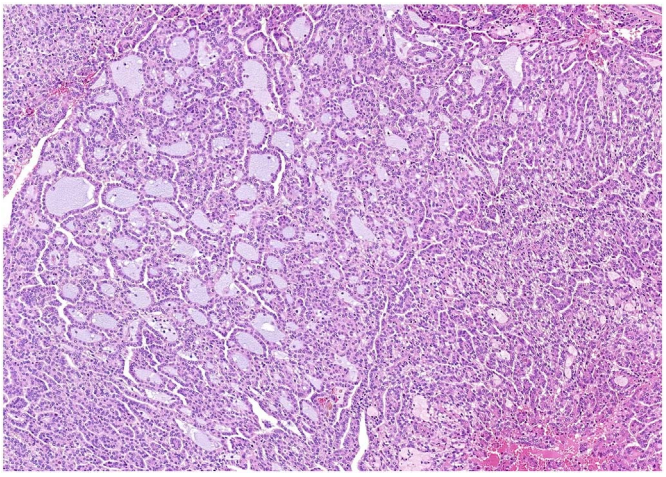

Fig. 4. Papillary renal cell carcinoma with mucicarmin positive deposition is a papillary lesion with areas containing bluish mucinous material.

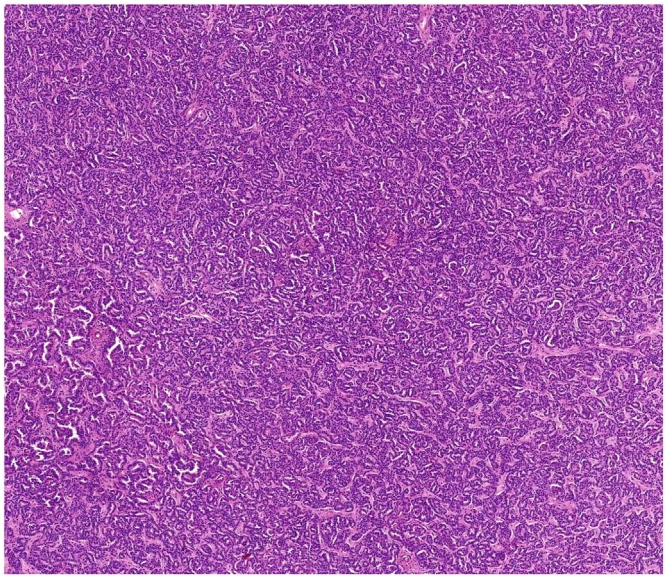

Fig. 5. So-called solid variant of papillary renal cell carcinoma is a compact tumor composed of small tubules, more or less compressed.

common features described in 66.7–100% of cases in different studies [5-10,42]. Loss of gonosome Y can be seen in 77.8–100% of male cases [7-10].

Numerical aberration status in PRCC type 2 is much more variable in contrast to PRCC type 1. In fact, the recent Cancer Genomic Atlas Research Network findings on PRCCs showed that PRCC type 1 and type 2 are clinically and biologically distinct tumors, with type 2 being consisted of at least three subtypes based on molecular features [42]. Nonetheless, the gains of chromosomes 7 and 17 are the most common molecular findings in PRCC type 2. These molecular changes are found in 31.2–69.2% (gain of chromosome 7) and 50–68.8% (polysomy of chromosome 17) in different studies. Other relatively frequent chromosomal changes in these tumors are polysomy of chromosomes 12, 16 and 20 [5-10]. Loss of gonosome Y is also described in 63.6–90% male cases of PRCC type 2 [7-9]. Further, there are a wide spectrum of CNAPs reported in PRCC type 2 (in smaller frequencies) including gains of chromosomes 1, 2, 3, 4, 5, 6, 8, 9, 13, 18, 19 and 22, as well as losses of chromosomes 1, 2, 3, 4,5, 6, 7, 8, 9, 10, 12, 13, 14, 15, 17, 18, 19, 20, 21, 22, and X [5-10].

A peculiar yet particularly interesting finding in chromosomal numerical aberration status has been recently reported in OPRCC. In a large scale study by Michalova et al. 43.5% of OPRCCs showed CNAP very similar to renal oncocytoma (RO). In this study, only 6/22 case (27.3%) showed polysomy of chromosomes 7 and 17. Given considerable CNAP overlap between OPRCC and RO, the reliability of CNAP analysis as a potential diagnostic utility tool in the differential diagnosis workup would be of major concern [14].

Molecular genetic studies performed in solid PRCC showed gains of chromosomes 7 and 17 and loss of chromosome Y in male patients in high percentage of cases (gain of chromosome 7 in 66.7–100% of cases, gain of chromosome 17 in 93.8–100% of cases, and loss of gonosome Y in 100% of cases) (Table 8) [22,24,25].

"Mucin" secreting PRCC is also composed of molecular-genetically heterogeneous tumors. A study by Pivovarcikova et al. demonstrated the gain of chromosomes 7 in 50% of cases, chromosome 17 in 75% of cases, chromosome 16 in 50% of cases, and the loss of chromosome Y in all male cases (100%). However, it should be noted that the sample size in the study was rather small, with only limited number of cases being suitable for genetic analysis [20].

BSARCCs showed numerical chromosomal abnormalities traditionally believed to be characteristic of PRCC. The largest series of BSARCCs, published by Hes et al. showed gains of chromosomes 7 and 17 in all

Table 7
Cystic and necrotic PRCC – chromosomal gains and losses.

		2+	3+	7+	9+	12+	13+	16+	17+	20+	21+	22+	7+,17+ in common	21-	Y-
Peckova et al. [21]	aCGH	1/7 14.3%	1/7 14.3%	3/7 42.9%	1/7 14.3%	3/7 42.9%	1/7 14.9%	2/7 28.6%	4/7 57.1%	2/7 28.6%	1/7 14.3%	1/7 14.3%	3/7 42.9%	1/7 14.3%	2/6M 33.3%
	FISH			5/8 62.5%					6/8 75%				5/8 52.5%		5/7M 71.4%

Table 8
Solid PRCC – chromosomal gains and losses.

		3+	5+	7+	12+	16+	17+	20+	X+	7+17+ in common	Y-	14-	18-	21-
Renshaw et al. [22]	FISH			2/3 66.7%			3/3 100%			2/3 66.7%				
	Cytogenetic study	1/1 100%	1/1 100%		1/1 100%	1/1 100%	1/1 100%	1/1 100%	1/1 100%			1/1 100%	1/1 100%	1/1 100%
Zhang et al. [25]	FISH			2/2 100%			2/2 100%			2/2 100%	2/2 100%			
Mantoan Padilha et al. [24]	FISH			14/16 87.5%			15/16 93.8%			13/16 81%	NP			

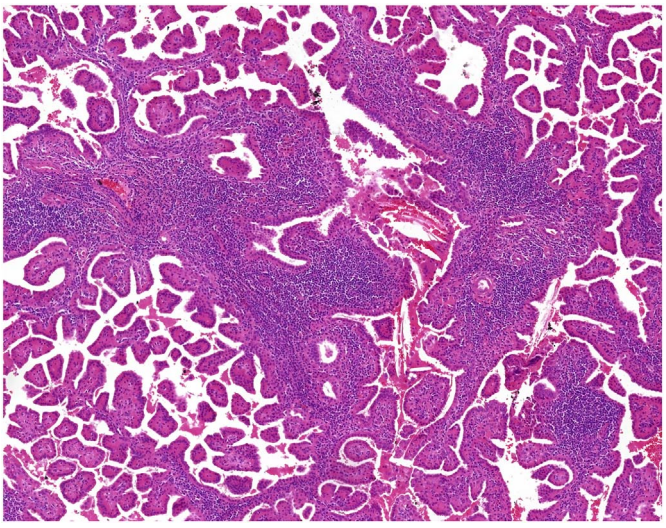

Fig. 6. Warthin-like variant of papillary renal cell carcinoma is a recently described lesion composed of papillary structures with dense lymphoid stroma and oncocytic cells on the surface of papillae.

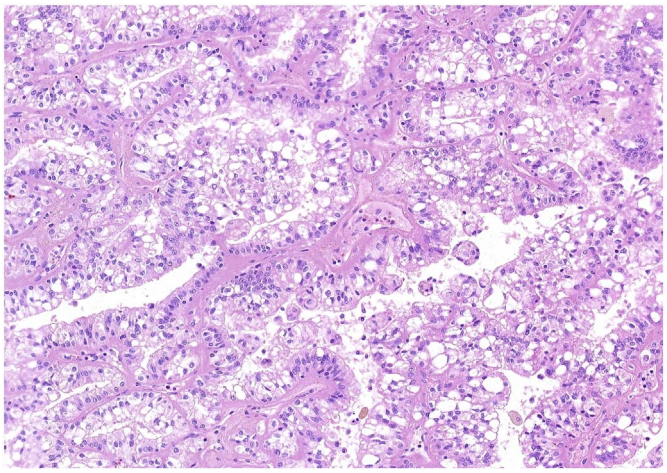

Fig. 7. Papillary renal cell carcinoma with clear cells is a tumor different from clear cell papillary renal cell carcinoma. Tumor is composed of clear cells admixed with cells with granular eosinophilic cytoplasm.

analyzable cases (100%) and the loss of chromosome Y in 80% of male patients. Other chromosomal abnormalities described in this study are presented in Table 11. The high percentage of polysomy of chromosomes 7 and 17 can be explained by the fact that some of these tumors histologically exhibited features compatible with PRCC type 1 [32].

All published studies on PRCC with clear cell changes strictly used results of molecular genetic analysis in classification of these tumors; CNAP was used as an ultimate criterion for the classification of such tumors in these studies [27,29-31]. Fuzesi and Salama presented RCCs with papillary architecture and clear cells, which were classified as clear cell renal cell carcinoma based on cytogenetic finding of loss of terminal 3p chromosomal segment [29,30]. Gobbo et al. assessed 14 RCCs with papillary architecture and clear cells, of which 9 were classified as PRCC based on cytogenetic changes including gains of chromosomes 7 (88.9%) and/or 17 (88.9%) and loss of chromosome Y in all male cases (100%). 3/14 cases in this study were classified as CCRCC (cases with detected 3p deletion), and 2/14 cases remained as unclassified (one case had polysomy of chromosomes 7 and 17 and 3p deletion, one case showed no changes in these three monitored parameters) [27]. Haudebourg's group had similar approach in their three cases included in the study. Two cases with detected polysomy 7 and 17 were labeled as PRCC. One case with polysomy of chromosomes 7 and 17 and concurrently LOH of chromosome 3 was designated as "unclassified RCC" [31].

Warthin-like PRCC has a wide spectrum of chromosomal changes and it is evident that this subgroup is rather heterogeneous. Only one described case of Warthin-like PRCC showed polysomy of chromosomes 7 and 17, which is believed to be characteristic for PRCC. Some published cases had no chromosomal changes, while other cases showed non-characteristic gains and losses of different chromosomes [26].

Table 9
Warthin-like PRCC – chromosomal gains and losses.

		1+	2+	5+	7+	8+	12+	17+	21+	1-	3-	14-	15-	18-	22-	Y-	X-
Skenderi et al. [26]	Low pass whole genome sequencing	1/9 11.1%	1/9 11.1%	2/9 22.2%	1/9 11.1%	1/9 11.1%	1/9 11.1%	1/9 11.1%	1/9 11.1%	3/9 33.3%	2/9 22.2%	2/9 22.2%	1/9 11.1%	1/9 11.1%	1/7 14.3%	2/7M 28.6%	1/7 14.3%

Table 10
PRCC with clear cell changes – chromosomal gains and losses.

		3p-	2+	3+	4+	5+	7+	9+	11+	12+	13+	16+	17+	18+	20+	21+	22+	7+17+ in common	7-	9-	13-	14-	17-	21-	22-	Y-
Gobbo et al. [27]	FISH	0/9 0%					8/9 88.9%						8/9 88.9%					7/9 77.8%								4/4 100%
Fuzesi et al. [29]	Karyotyping	3/3 100%					1/3 33.3%			1/3 33.3%					1/3 33.3%					1/3 33.3%	1/3 33.3%	3/3 100%		1/3 33.3%	1/3 33.3%	
Salama et al. [30]	FISH + microsatellite Analysis	6/7 85.7%					0/6						0/6						4/6 67%				6/6 100%			
Haudebourg et al. [31]	FISH	0	1/3 33.3%	1/3 33.3%			3/3 100%	1/3 33.3%					3/3 100%	1/3 33.3%				3/3 100%								1/1 100%
	SNP array	1/2 50%	2/2 100%	1/2 50%	1/2 50%	1/2 50%	2/2 100%	1/2 50%	1/2 50%	1/2 50%	1/2 50%	1/2 50%	2/2 100%	1/2 50%	1/2 50%	1/2 50%	1/2 50%	2/2 100%								1/1 100%

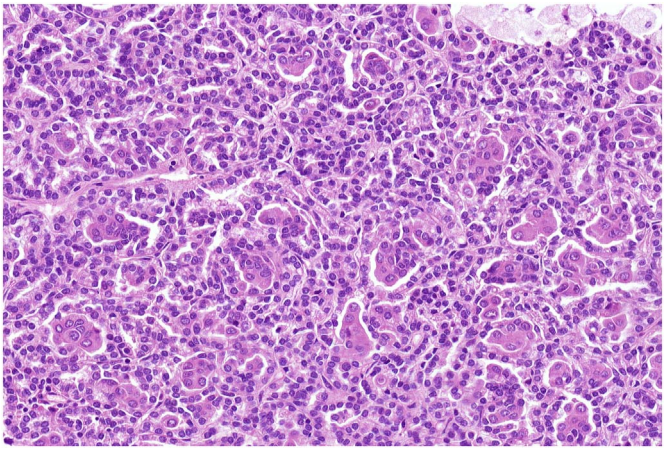

Fig. 8. Biphasic squamoid alveolar (papillary) renal cell carcinoma is a recently described variant, which is composed of dual cell population: small low-grade cells with scanty cytoplasm and large high grade eosinophilic cells almost identical to squamous cells.

Molecular-genetic analysis of cystic and necrotic PRCC showed polysomy of chromosome 7 (62.5% cases) and polysomy of chromosome 17 (75% cases). Loss of chromosome Y was detected in 71.4% of male patients. There were other chromosomal abnormalities reported in these tumors, while no chromosomal numerical aberrations were found in some cases [21]. These findings are somewhat surprising given all cystic and necrotic PRCCs were histologically consistent with PRCC type 1 in viable and preserved areas, where higher percentage of polysomy chromosomes 7 and 17 would have been expected.

Overall, this review highlights the fact that PRCC is composed of a highly heterogeneous group of tumors with broad morphological spectrum and immunohistochemical profile. This fact has also recently been supported by Salleeb et al. [43]. The authors showed high variability and heterogeneity among PRCCs as a group of tumors and proposed 2 new subtypes [43]. From all above mentioned facts, it is evident that chromosomal numerical aberration status is much more complex than traditionally thought. Of all PRCC subtypes/variants, PRCC type 1 seems to be a genetically uniform group, while other types showed different degrees of heterogeneity. We believe that it may not be possible to distinguish various PRCC subtypes merely based on CNAP. In other words, CNAP should be considered only as one of diagnostic tools (like immunohistochemistry) in clinical decision making process. Finally, it is becoming more evident that tumor type-specific chromosomal numerical aberration status in PRCCs may not exist.

Disclosure of conflict of interest

All authors declare no conflict of interest.

Table 11
Biphasic squamoid alveolar RCC – chromosomal gains and losses.

		1+	5+	7+	11+	12+	13+	16+	17+	20+	7+,17+ in common	2-	5-	6-	9-	12-	15-	16-	17-	18-	21-	22-	Xp-	Y-
Hes et al. [32]	Array CGH			5/5 100%		1/5 20%		1/5 20%	5/5 100%	3/5 60%	5/5 100%										1/5 20%		1/5 20%	
	FISH			11/11 100%					11/11 100%		11/11 100%													4/5M 80%

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