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Review

Review of papillary renal cell carcinoma with focus on clinical and pathobiological aspects

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Summary. Recent studies have shown that papillary renal cell carcinoma (RCC) is clinically and genotypically a distinct entity. Papillary RCCs account for about 10-15% of renal parenchymal neoplasms. Macroscopically, the cut surface is yellow or brown in color and large tumors frequently show cystic change. Hemorrhage and necrosis are common. Histologically, Delahunt and Eble have classified papillary RCCs into type 1 (small cells, single layer) and type 2 (large cells, pseudostratification) according to the cytoplasmic volume and thickness of the lining cells. In chromosomal analysis, gain of chromosomes 7 and 17, loss of Y chromosome and additional gains (chromosome 3q, 8p, 12q, 16q and 20q) are frequently found in type 1 papillary RCCs, but the chromosomal aberration of type 2 papillary RCCs seems to be more heterogenous than that of type 1 papillary RCCs. Mutations of MET proto-oncogenes in some cases of both hereditary and sporadic papillary RCCs have recently been detected. Furthermore, all hereditary and sporadic papillary RCCs with MET proto-oncogene show type 1 histological features. Type 1 papillary RCCs generally seem to have a favorable prognosis, but type 2 tumors have a worse prognosis than do type 1 tumors. Papillary RCCs with involvement of the X chromosome and cancer syndrome with predisposition to cutaneous/uterine leiomyomas and papillary RCCs, the histological features of which are basically different from those of usual papillary RCCs, have also been recently reported. Since papillary RCCs seem to constitute clinically, histologically, and even genetically more heterogenous groups than previously thought, further investigations are needed to characterize the subtype of papillary RCC.

Key words: Papillary renal cell carcinomas, Pathology, Chromosomal abnormalities

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History of the establishment of the disease concept

Mancilla-Jimenez et al. reported in 1976 that patients with papillary RCCs have longer survival than patients with conventional (nonpapillary) RCCs, both overall and stage-for-stage. This finding has been supported by results of subsequent clinicopathological studies (Blath et al., 1976; Boczko et al., 1979; Mydlo and Bard, 1987). Kovacs et al. recognized papillary RCC as a genotypic distinct entity since they found that papillary tumors with alterations in three chromosomes (+7, +17, and -Y) generally have a benign clinical course, whereas papillary tumors with additional trisomies (+16, +12 or +20) usually behave in an aggressive fashion (Kovacs, 1989; Kovacs et al., 1991). In contrast to papillary RCCs, almost all conventional RCCs show a deletion of the 3p segment (Kovacs and Frisch, 1989; Kovacs and Kung, 1991; Kovacs, 1993). In recent classifications, papillary RCCs have been regarded as a separate entity (Kovacs et al., 1997; Störkel et al., 1997). Furthermore, in contrast to the frequent inactivation of VHL tumor suppressor gene in conventional RCCs, mutations of MET proto-oncogene in some cases of both hereditary and sporadic papillary RCCs have recently been detected (Schmidt et al., 1997, 1998, 1999; Fischer et al., 1998; Lubensky et al., 1999).

Epidemiology

Papillary RCCs comprise approximately 10-15% of renal parenchymal neoplasms (Kovacs et al., 1997; Störkel et al., 1997). The mean age and range of ages with RCCs were 61.8 years and 22-83 years, respectively, in a study by Amin et al. (1997) and 57 years and 5-82 years, respectively, in a study by Delahunt and Eble (1997).

Clinical symptoms and signs

Hematuria, abdominal pain and abodminal mass are often observed (Mancilla-Jimenez et al., 1976; Blath et al., 1976; Boczko et al., 1979; Mydlo and Bard, 1987). Some tumors are discovered incidentally (Blath et al.,

1976; Boczko et al., 1979; Mydlo and Bard, 1987).

Other clinical settings

Ishikawa et al. (Ishikawa and Kovacs, 1993a; Ishikawa et al., 1993b) reported that the incidence of papillary RCCs in long-term hemodialysis patients is high. A case of papillary RCC arising in an allografted kidney has been reported (Niranjan et al., 1999). Recently, hereditary papillary RCCs have been reported (Zbar et al., 1994, 1995).

Radiological findings

Ultrasound sonography reveals a necrotic or cystic tumor (Mancilla-Jimenez et al., 1976). A selective renal arteriogram shows a hypovascular or avascular mass (Mancilla-Jimenez et al., 1976; Boczko et al., 1979; Mydlo and Bard, 1987). Calcification is also occasionally observed (Mancilla-Jimenez et al., 1976; Krieger et al., 1979).

Pathological findings

Macroscopic findings

Papillary RCCs form well-circumscribed masses and frequently have thick fibrous capsules or pseudocapsules (Mancilla-Jimenez et al., 1976; Amin et al., 1997). The mean size and range of sizes of tumors were 6.7 cm and 1.8-18 cm , respectively, in a study by Amin et al. (1997) and 7.2 cm and 1.2-26 cm, respectively, in a study by Delahunt and Eble (1997). Small tumors are usually solid, and large tumors frequently show cystic change (Amin et al., 1997). The cut surface is yellow or brown in color (Mancilla-Jimenez et al., 1976; Amin et al., 1997). Hemorrhage and necrosis are frequently seen (Mancilla-Jimenez et al., 1976; Amin et al., 1997). Multifocal tumors are frequently observed (Kovacs, 1989; Kovacs et al., 1991; Kovacs and Kovacs, 1993; Amin et al., 1997).

Microscopic findings

A variety of architectural patterns such as papillary, tubular, trabecular and solid are observed in papillary RCCs (Amin et al., 1997; Renshaw and Corless, 1995; Renshaw et al., 1996, 1997b). Sarcomatoid transformation of papillary RCCs have been reported (Ro et al., 1987). Classically, tumors have been classified as papillary RCCs if papillary structures comprise at least 50% of the tumor (Mancilla-Jimenez et al., 1976). However, Kovacs et al. suggested that more than 75% of the tumor being composed of papillary structures may be a better criteria for discriminating papillary RCCs from nonpapillary RCCs showing 3p deletions (Kovacs, 1989; Kovacs et al., 1991). On the other hand, Renshaw et al. (1997b) found the presence of solid variants of papillary RCCs that are composed of

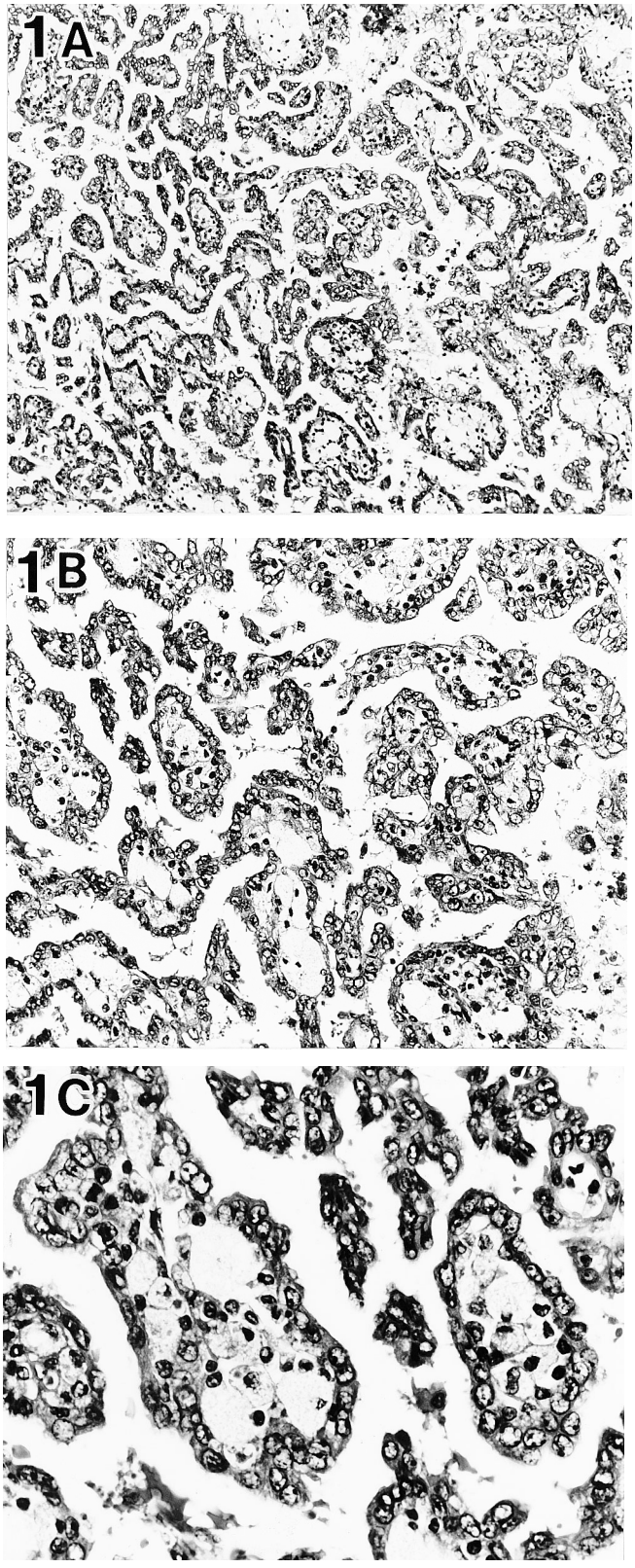

Fig. 1. Histological features of type 1 papillary RCC. Tumor cells with scanty basophilic cytoplasm have proliferated with papillary growth. Nuclei are arranged in a single layer. a, x 25; b, x 50; c, x 100

poorly formed papillae. However, they estimated that this group comprises at most <3% in all papillary RCCs. Cytologically, cytoplasmic features including eosinphilic, basophilic and mixed populations have been described (Amin et al., 1997). In the fibrovascular core or the stroma, foamy macrophages, hemosiderin deposition or calcification is occasionally observed (Mancilla-Jimenez et al., 1976; Renshaw et al., 1995; Amin et al., 1997). Papillary RCCs have been divided into low grade (grades 1 and 2) and high grade (grades 3 and 4) according to the nuclear grade classification by Lager et al. (1995) and Renshaw and Corless (1995) and into type 1 (small cells, single layer) and type 2 (large cells, pseudostratification) according to the cytoplasmic volume and thickness of the lining cells by Delahunt and Eble (1997). Mucin production is rarely seen (Val-Bernal et al., 1998, 1999). Since the development of papillary RCCs is associated with multiple precursor lesions resembling nephrogenic rests, Kovacs and Kovacs (1993) suggested that papillary RCCs originate from embryonal tissue.

Histochemical and immunohistochemical findings

Patterns of lectin biding to *Lotus tetragonobulus* agglutinin (LTA), soybean agglutinin (SBA), *Dolichos biflorus* agglutinin (DBA) and peanut agglutinin (PNA) are variable (Ulrich et al., 1985). However, *Ulex europaeus* lectin (UEA-1) is consistently negative for papillary RCCs, in contrast to collecting duct carcinomas (CDCs) (Delahunt and Eble, 1997). Although Gatalica et al. (1995) reported that cytokeratin 7 was found to be consistently expressed in papillary RCCs, Delahunt and Eble (1997) found that the expression of cytokeratin 7 is more frequent in type 1 tumors than in type 2 tumors. The immunoreactivity for vimentin is variable, but vimentin expression is greater in type 1 tumors than in type 2 tumors (Delahunt and Eble, 1997). Immunohistochemically, papillary RCCs show the phenotype of both proximal and distal nephrons (Hughson et al., 1993; Kuroda et al., 1998b, 2000b). de Peralta-Venturina et al. (1994) reported that information on the proliferative activity, such as the activity of proliferating cell nuclear antigen (PCNA) and Ki-67 (MIB-1), assessed by immunohistochemistry is not useful for predicting the outcome of papillary RCC. On the other hand, Delahunt et al. (2001) showed that AgNOR score and Ki-67 index are independently associated with survival by using multivariate analysis.

Ultrastructural findings

Ultrastructurally, tumor cells contain only a few organelles and lipid droplets (Störkel, 1995, 1996). Only a few or no glycogen deposits are observed in the tumor cytoplasm (Störkel, 1995, 1996; Krishnan and Troung, 2002). In eosinophilic variants, accumulation of mitochondria is observed in the cytoplasm (Krishnan and Troung, 2002). In contrast to long microvilli in

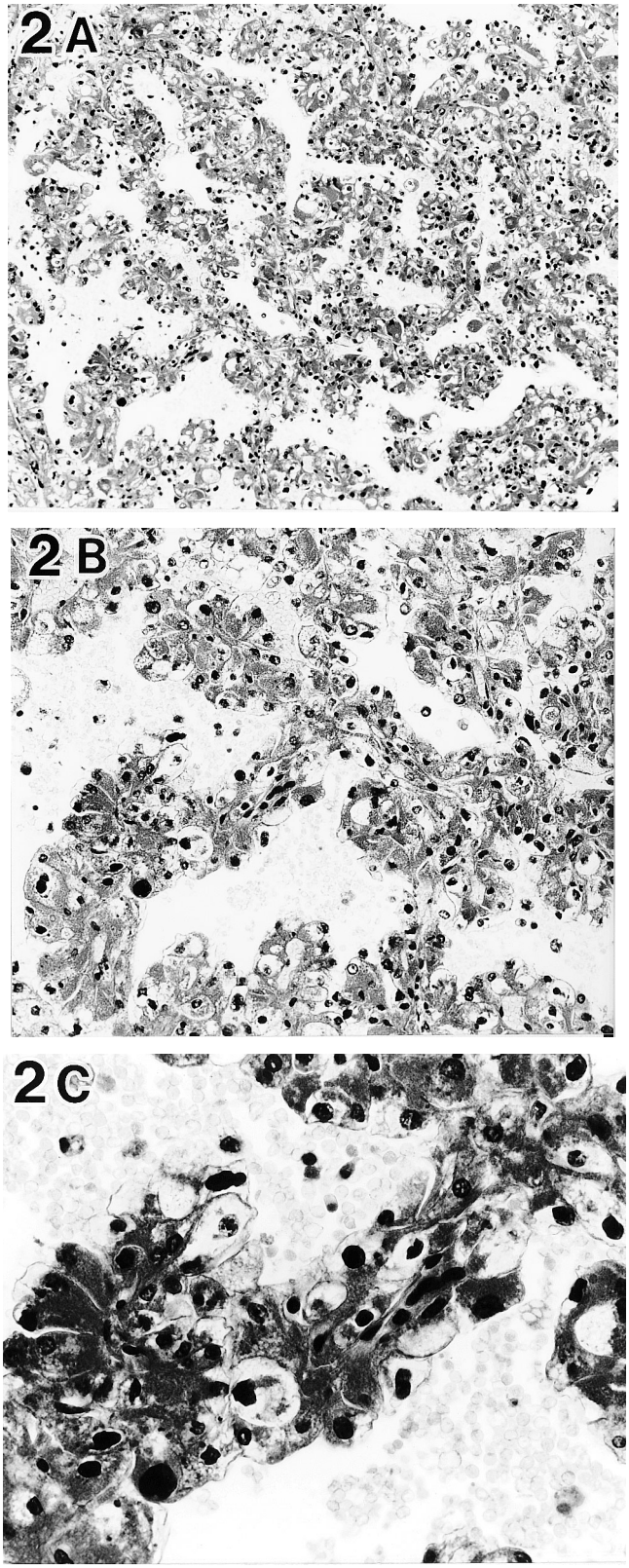

Fig. 2. Histological features of type 2 papillary RCC. Tumor cells with abundant eosinophilic cytoplasm have proliferated with papillary growth. Nuclei exhibit psuedostratification. a, x 25; x 50; x 100

conventional RCCs, various-sized microvilli along the apical cell membrane may be observed in papillary RCCs (Krishnan and Troung, 2002).

Cytological findings

In fine-needle aspiration specimens, tumor cells have moderate to scant cytoplasm, nuclei are usually small and uniform, mild to moderate hyperchromasia is common, nucleoli are single and small, and nuclear grooves are often prominent (Flint and Cookingham, 1987; Dekmezian et al., 1991; Weaver et al., 1991). Foamy macrophages in the background and intracellular hemosiderin and psammoma bodies are occasionally seen (Flint and Cookingham, 1987; Dekmezian et al., 1991; Weaver et al., 1991). These are also observed in cytobrush scraping specimens but not in voided urine cytology due to poor preservation (Kobayashi et al., 2000; Kawakami et al., 2001).

Flow cytometric analysis

In a study by El-Naggar et al. (1993), DNA aneuploidy was found in 50% of papillary RCCs. According to the report by del Vecchio et al. (1998), diploid and aneupolid patterns are observed in 35% and 65% of tumors, respectively.

Chromosomal analysis

In karyotyping, Dal Cin et al. (1988) suggested the presence of a subgroup of renal cell tumors with a combination of chromosomal aberrations (+7, +7, +17, -Y) that may originate from cortical adenomas. Kovacs (1993) and Kovacs et al. (1991) showed that tumors with a combination of tri- or tetrasomy of 7, trisomy of 17 and loss of Y are papillary adenomas and that papillary RCCs are characterized by additional trisomies of 16, 12 or 20. Most of the papillary RCCs in these studies seem to be histologically type 1 tumors according to the classification of Delahunt and Eble (1997). On the other hand, Füzesi et al. (1999) reported three cases of papillary RCCs with clear cell cytomorphology showing loss of 3p but not trisomy of 17, and they therefore concluded that papillary RCCs should be classified according to their cytomorphology rather than their growth pattern. Renshaw et al. (1997a) reported that trisomy of 3 was occasionally detected in papillary RCCs and that this aberration is associated with low-grade, low-stage tumors with intracytoplasmic hemosiderin. Using FISH, Kattar et al. (1997) found the existence of two groups, one consisting of typical aberrations with gains of 7 and 17 and loss of Y, and the other consisting of cytogenetically atypical tumors. Lager et al. (1995) reported that tisomy of 7 by FISH was found by FISH analysis in 67% of low-grade cancers and in 43% of high-grade cancers. Using CGH, Jiang et al. (1998) found that gains of 7p and 17p are significantly higher in type 1 tumors than in type 2 tumors by the classification of Delahunt and Eble (1997). Bentz et al. (1996) reported that the results of CGH analysis revealed frequent occurrence of gain of chromosomes 7 and 17 in sporadic and hereditary papillary RCCs. By microsatellite analysis of 34 papillary RCCs, Palmedo et al. (1997) detected allelic duplications of 7q31-33 (in 64% of the RCCs), 17q12-22 (in 70%), 16q24-qter (in 55%), 12q12-14 (in 42%), 8p21 (in 25%), 3q22-24 (in 24%), and 20q13 (in 48%) and loss of Y (in 74%). They also found that allelic duplications at 20q11.2 and 20q13.2 frequently occur in papillary RCCs (Palmedo et al., 1999). Using microsattelite analysis, Balint et al. (1999) have found that allelic duplication at 17q21.32 frequently occurs in papillary RCCs . Schraml et al. (2000) reported that LOH at D9S171 (9q13) was detected in 21% of papillary RCCs and that this change is associated with short survival.

In summary, gain of chromosomes 7 and 17, loss of Y chromosome and additional gains (chromosome 3q, 8p, 12q, 16q and 20q) are frequently observed in type 1 papillary RCCs by the classification of Delahunt and Eble (1997), but the chromosomal aberration of type 2 papillary RCCs seems to be more heterogenous than that of type 1 papillary RCCs.

Involvement of oncogene or tumor supressor gene

Schmidt et al. (1997) reported that missense mutation in the tyrosine kinase domain of the MET proto-oncogene in chromosome 7q31 was detected in hereditary papillary RCCs. Fischer et al. (1998) found that the duplicaton and overexpression of mutant alleles of MET proto-oncogene occurs in hereditary papillary RCCs. These mutations frequently occur in exons 17, 18, and 19 and occasionally in exon 16 (Schmidt et al., 1997, 1998). Schmidt et al. (1999) also found mutations of the MET proto-oncogene in 13% of sporadic papillary RCCs, about half of which were germ-line mutations and the remaining somatic mutations. Lubensky et al. (1999) found that all hereditary and sporadic papillary RCCs with MET proto-oncogene show type 1 histological features by the classification of Delahunt and Eble (1997). However, not all type 1 papillary RCCs have mutations of the MET proto-oncogene (Schmidt et al., 1999). Recently, epigenetic inactivation of the RASSF1A gene at the 3p21.3 locus by frequent hypermethylation has been found in both papillary and conventional RCCs (Morrissey et al., 2001).

Papillary RCCs with involvement of X chromosome

Some cases of papillary RCCs with involvement of Xp11 have been reported. These cases showed t(X;1)(p11.2;q21), t(X;1)(p11.2;p34), t(X;10)(p11.2;q23), t(X;17)(p11.2;q25.3) and del (X)(p11) (Meloni et al., 1993; Dijkhuizen et al., 1995, 1998; Hernandez-Marti et al., 1995; Tonk et al., 1995; Dal Cin et al., 1998; Perot et al., 1999; Morrissey et al., 2001;

Zattara-Cannoni et al., 2001). Among them, cases showing t(X;1)(p11.2;q21) have frequently been reported. This translocation occurs in both young people and adults (Meloni et al., 1993; Tonk et al., 1995; Dal Cin et al., 1998; Dijkhuizen et al., 1998; Perot et al., 1999; Morrissey et al., 2001; Zattara-Cannoni et al., 2001). The histological features of tumors with this translocation are also different from those of usual papillary RCCs (Tonk et a., 1995; Dal Cin et al., 1998; Dijkhuizen et al., 1998; Perot et al., 1999; Zattara-Cannoni et al., 2001). In t(X;1)(p11.2;q21.2)-positive papillary RCCs, fusion of the transcription factor TFE3 gene to the novel gene PRCC has been observed (Sidhar et al., 1996; Weterman et al., 1996). Similarly, in t(X;17)(p11.2;q25.3)-positive papillary RCCs, fusion of the novel gene RCC17 to the TFE3 gene has been observed (Heimann et al., 2001).

Cancer syndrome with predisposition to cutaneous/uterine leiomyomas and papillary RCCs

Launonen et al. (2001) and Kiuru et al. (2001) recently reported a cancer syndrome with predisposition to cutaneous or uterine leiomyomas and papillary RCCs. They reported that this gene is mapped to chromosome 1q42-q44 and is considered to be a tumor suppressor.

Differential diagnosis in histopathology

Differentiation from CDCs, conventional RCCs, eosinophilic variants of chromophobe RCCs, metanephric adenomas, oncocytomas and juxtaglomerular tumors is important. Among them, the distinction from CDCs is most important. Macroscopically, the cut surfaces of CDCs, conventional RCCs, chromophobe RCCs and oncocytomas are typically white or gray, yellow, beige and mahogany brown in color, respectively. Metanephric adenomas show a yellow or gray color (Störkel, 1995, 1996). Microscopically, if papillary structures are prominent, the possibility of conventional RCCs, chromophobe RCCs and oncocytomas can be ruled out. However, papillary projection may be present in CDCs, metanephric adenomas or juxtaglomerular cell tumors. CDCs are characterized by a variety of cytological and histological appearances (Störkel 1995, 1996; Kuroda et al., 2001b). Abnormal mitotic figures are never observed in oncoytomas or metanephric adenomas. Histochemically or immunohistochemically, CDCs show UEA-1 and high-molecular-weight cytokeratin (34ßE12), whereas papillary RCCs are generally negative for them (Kuroda et al., 2001b). Ultrastructurally, chromophobe RCCs, oncocytomas and juxtaglomerular cell tumors contain many microvesicles, many mitochondria and renin granules in the cytoplasm, respectively (Störke, 1995, 1996; Kuroda et al., 1998a, 2000a, 2001a,b). Chromosomal analysis may also be useful for differential diagnosis. Conventional RCCs show a loss of 3p segment, and chromophobe RCCs show a low chromosome number (Kovacs and Frisch, 1989; Kovacs and Kung, 1991; Kovacs, 1993). In contrast, trisomy of chromosomes 7 and 17 is often seen in papillary RCCs (Kovacs, 1989; Kovacs et al., 1991). However, microsatellite analysis has shown that some cases of papillary RCCs have a deletion of chromosome 3p (Corless et al., 1996; Hughson et al., 1996, 1998; Schraml et al., 2000).

Treatment and prognosis

Radical, simple, or partial nephrectomy is generally performed (de Peralta-Venturina et al., 1994; Amin et al., 1997). Results regarding the clinical outcome of papillary RCCs are conflicting. Some investigators have reported that papillary RCCs have a favorable prognosis compared with that of conventional RCCs (Blath et al., 1976; Mancilla-Jimenez et al., 1976; Boczko et al., 1979; Mydlo and Bard, 1987; Amin et al., 1997), but others have reported no difference in prognosis or even worse prognosis (Fuhrman et al., 1982). Delahunt et al. (2001) and Jiang et al. (1998) reported that type 2 tumors have a worse prognosis than type 1 tumors and that the 5-year survival rate for patients with the former is similar to that for patients with conventional RCCs.

Conclusions and perspectives

Based on the above-described findings, papillary RCC can be regarded as a distinct entity both in terms of morphology and molecular genetics. However, on the basis of results of recent studies, papillary RCCs seem to constitute clinically (age distribution and clinical behavior), histologically, and even genetically more heterogenous groups than previously thought. The concept of papillary RCC may therefore be subdivided into various entities in the near future. Furthermore, some papillary RCCs are difficult to distinguish from collecting duct carcinomas in routine histological examinations. Further studies are therefore needed to identify the gene responsible for the development of papillary renal cell tumors and to completely elucidate the clinicopathological characteristics.

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