Papillary cell renal carcinoma. Radiological findings and pathological correlation.

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Learning objectives

• List the imaging features that help characterize papillary cell renal carcinomas (PRCC).
• Describe the histological features and correlate them with the radiological characteristics.
Background

INTRODUCTION

Renal cell carcinomas (RCC) represent 3% of malignant tumors in adults. 70% are incidentally detected.

Papillary renal cell carcinoma (PRCC) is the second most common RCC after clear cell carcinoma (10-15%). Among the non-clear-cell subtypes, PRCC constitutes approximately 50-65% of cases.

There are two histological subtypes of PRCC. Type-1 are usually low grade and less aggressive tumors, whereas type-2 often harbour atypia and have a poor prognosis.

There are conflicting data regarding whether histological subtyping of PRCC represents an independent prognostic factor irrespective of the tumor stage and nuclear grade.

HISTOLOGY

Type 1 PRCC (Fig. 1 on page 7) are slightly more frequent. These tumors have small cells with scanty pale cytoplasm and small, uniform, oval nuclei, arranged in a single layer on the basement membrane of papillary cores. It is the most frequently multifocal RCC. Type 1 tumors are more likely to have solid architecture and lower nuclear grades.

In a recent study of immunohistochemical stains on 124 PRCC, Type 1 tended to bear higher expression rates of CK7, EMA, and Racemase, with CK7 and EMA reaching statistical significance.

Type 2 tumors (Fig. 2 on page 7) have cells that are larger and have pseudostratified large, spherical and irregular nuclei with prominent nucleoli, and usually exhibit voluminous eosinophilic cytoplasm. Necrotic and hemorrhagic degeneration are relatively common. Nuclear grades are usually higher.

Type 2 PRCC tended to bear higher expression rates of CD10 and PAX-2, with CD10 reaching statistical significance. There is also usually intense and diffuse membrane immunostaining for e-cadherin.

The expression rates of CAIX, CK903, C-kit, PAX-8, and CEA were fairly comparable in the 2 subtypes.

Sarcomatoid differentiation is exceptional in PRCC, although it has been described in some type 2 tumors (Fig. 3 on page 8).
Approximately 17% of PRCC show mixed histological features between types 1 and 2. The existence of such mixed lesions and the overlapping in immunohistochemical behaviour suggest that there might be a common origin for both types. It has been suggested that PRCC may have developed from nephrogenic rest-like lesions.

STAGING AND PROGNOSIS

**Type 1 PRCC.** Tumor grades are almost constantly low (99% grades 1 and 2). Infiltration of perirenal or sinus fat, venous extension and lymphadenopathy are very infrequent. The occurrence of distant metastases at diagnosis is only 1-3.7%.

**Type 2 PRCC.** Nuclear grades are commonly high (69% 3 and 4). Nodal, fat and venous extension, although not frequent, is not exceptional (15, 4 and 4 % respectively). Distant metastases are present in 7.5-13% of cases.

Recent studies have not reported any correlation between immunohistochemical expression and outcome, except for p53, which was shown to be more prevalent in type 2 PRCC and strongly associated to poor survival.

There are conflicting data regarding whether histological subtyping of PRCC represents an independent prognostic factor irrespective of the tumor stage and nuclear grade.

GENETICS AND MOLECULAR FEATURES

After comprehensive molecular characterization of 161 primary PRCC, the Cancer Genome Atlas Research Network has demonstrated that Type 1 and type 2 PRCC are shown to be different types of renal cancer characterized by specific genetic alterations, with type 2 further classified into three individual subgroups on the basis of molecular differences associated with patient survival.

**Type 1** tumors are associated with MET alterations in 81% of cases, although somatic MET mutations occur only in 13 to 15% of nonhereditary PRCC.

**Type 2** tumors are more heterogeneous and characterized by CDKN2A silencing, SETD2 mutations, TFE3 fusions, and increased expression of the NRF2-antioxidant response element (ARE) pathway.

MULTIPLE PRCC AND PRCC IN HEREDITARY SYNDROMES

PRCC type 1 are the most frequent renal tumors to be sporadically multiple and bilateral.

**Hereditary papillary renal cell carcinoma (HPRCC)** is an autosomal dominant syndrome with high penetrance (90% probability of developing cancer by age 80 years). Morphologically these tumors always belong to type 1 PRCC and are frequently
multifocal. HPRCC was linked to abnormalities at chromosome 7q31.3, and was subsequently associated with oncogenic activation of the mesenchymal epithelial transition (MET) gene. Although germ line MET proto-oncogene mutations are the hallmark of HPRCC, somatic MET mutations in sporadic PRCC occur in only 5% to 13% of cases. However, most patients with sporadic type 1 PRCC harbor duplication of chromosome 7, or amplification of the region where MET is located, indicating a likely alternative mechanism for MET activation in sporadic PRCC.

Hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome is associated with cutaneous and uterine leiomyomatomas and in approximately 20% of cases with PRCC, predominantly of type 2 morphology. HLRCC-associated renal tumors are typically solitary and unilateral but their nuclear grade is high (Furhman 3-4) and prognosis poor. Genetic alterations associated with HLRCC were mapped to chromosome 1q42.3-q43 and correspond to the fumarate hydratase (FH) gene. FH is an enzyme in the Krebs cycle that catalyzes the conversion of fumarate to malate. In sporadic type 2 PRCC, somatic FH mutations are rare and the molecular abnormalities are very heterogeneous.

Papillary thyroid cancer-papillary renal neoplasm (PTC-PRN) syndrome is an uncommon autosomal dominant hereditary condition that usually affects women. Secondary to a mutation in fPTC/PRN gene, papillary thyroid carcinoma, PRCC type 1 and papillary renal adenomas develop.

Other hereditary syndromes. PRCC may also appear in the context of Phosphatase and tensin homologue (PTEN) hamartoma tumor, Hereditary hyperparathyroidism-jaw tumor and Birt-Hogg-Dubé syndromes.

TREATMENT

PRCC are usually diagnosed in early stages and the cornerstone of management is surgery, which is commonly curative in these cases. A nephron-sparing strategy is especially necessary in cases of multifocal tumors.

Although the treatment of advanced clear-cell RCC has undergone dramatic changes with the introduction of mammalian target of rapamycin (M-TOR) inhibitors (temsirolimus, everolimus), and tyrosine kinase inhibitors of VEGF receptor (VEGFR) and its relatives (sunitinib, sorafenib, bevacizumab), optimal management of PRCC and other non-clear-cell histologies remain undefined.

Overall, the analysis of available data suggest that clinical benefit of currently available agents targeting VEGF pathways, although present in PRCC, is significantly inferior to that observed in clear cell histology. M-TOR inhibitors appear to have similar activity in patients with clear-cell RCC and non-clear histology including PRCC.
Clinical experience with MET inhibitors (tivantinib or ARQ-197), dual MET and VEGFR 2 inhibitors (foretinib), EGFR inhibitor (erlotinib) and dual EGFR and MET inhibition in PRCC is now beginning to emerge.

A significant proportion of PRCC (particularly type 2) does not demonstrate any derangements in MET. The recent substratification of type 2 PRCC according to specific molecular markers may allow more accurate diagnosis that could lead to the development of mechanistic, disease-specific targeted therapies.
**Fig. 1:** Typical histological and immunohistochemical findings in core needle biopsy of PRCC type 1. There are small cells with scanty pale cytoplasm and small, uniform, oval nuclei, arranged in a single layer on the basement membrane of papillary cores, without atypia (red arrows). The papillary cores contain macrophages with wide vacuolated cytoplasm (*) and small uniform nuclei. There is granular cytoplasmatic immunostaining with racemase inside the tumoral cells (black arrows). CK7 staining shows intense and diffuse cytoplasmatic positivity with focal membrane reinforcement.

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Fig. 2: Typical histological and immunohistochemical findings in PRCC type 2. 1. There is papillary architecture with extensive areas of necrotic and hemorrhagic degeneration (*) and prominent tumoral cells (white circle). 2. It may be occasionally difficult to visualize tumoral foci inside the necrotic tissue (black circle). 3. Tumoral cells that are larger than in type 1 PRCC, have pseudostratified large, spherical and irregular nuclei (white arrows) with prominent nucleoli, and usually exhibit voluminous eosinophilic cytoplasm. Nuclear grades are usually greater than in PRCC type 1. 4. Tumoral venous thrombus. Black arrows point to the thin venous wall. Blood (+) is present between the tumoral thrombus and the venous wall. 5. CD 10. Moderate cytoplasmic diffuse staining with apical membrane reinforcement. 6. Racemase. Intense granular cytoplasmic immunostaining in every tumoral cell. 7. E-Cadherin. Intense and diffuse membrane immunostaining. 8. CK 7 and EMA negative staining in tumoral cells.
**Fig. 3:** Area of solid sarcomatoid differentiation in PRCC type 2. There is a diffuse pattern of tumoral growth without a papillary architecture. Tumor cells exhibit nuclear pleomorphism (arrow), containing large and irregular nuclei with prominent nucleoli, frequent binucleate cells (arrowheads) and common mitotic figures (hollow arrows). Cytoplasm is wide and vacuolated (*).

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Findings and procedure details

We reviewed histologically proven cases of RCC diagnosed in the last seven years. Patients with PRCC represented 14%: 15 type 1, and 9 type 2 (Fig. 4 on page 15). There were no PRCC classified as mixed between types 1 and 2.

CT and US were performed to all 24 patients. Five patients with type I and three with type II underwent MRI. Contrast enhanced ultrasound (CEUS) was performed to six patients with type I and five with type 2 PRCC. Percutaneous biopsy led to diagnosis in four cases.

Computed Tomography exams were performed with a multiphase protocol, which included unenhanced, corticomedullary (35 secs.), nephrographic (70 secs.) and excretory (5-10 mins.) phases.

Clues for the abbreviations in figures:

H&E: Hematoxylin-Eosin stain. PRCC 1: Papillary renal cell carcinoma type 1; PRCC 2: Papillary renal cell carcinoma type 2; CCRC: Clear cell renal carcinoma; ChRCC: Chromofobe renal cell carcinoma. AML: Angiomyolipoma; Ax: axial; Cor: coronal; Sag: sagital or parasagital; UE: unenhanced; CM: corticomedully phase; NG: nephrographic phase; EX: excretory phase; HU: Hounsfield units; CT: Computed Tomography; US: Ultrasonography; CEUS: Contrast enhanced ultrasonography; fs: fat saturation; ip: in-phase; op: out-of-phase; Gd: gadolinium; Substr: substraction.

GENERAL FEATURES AND COMPUTED TOMOGRAPHY

The most common presentation of PRCC is a homogeneous (85%) encapsulated tumor (Fig. 5 on page 15). Only 2% show infiltrating growing. Most other renal solid non-fatty tumors are usually well defined encapsulated tumors, although some clear cell renal carcinomas (CCRC), especially those with sarcomatoid features, are infiltrative (Fig. 5 on page 15).

PRCC almost constantly exhibit low enhancement after intravenous contrast administration. Maximum enhancement is less than 40 HU in more than 80% of cases. (Fig. 6 on page 16). Variation in density is indeterminate (10-15 HU) or negative (less than 10 HU) in more than 20% of cases. It is very unlikely that a renal tumor reaching 100 UH in its solid components corresponds to a PRCC. The attenuation is usually maximal on the nephrographic phase of the study (60-120 seconds from the injection).

As a general rule, CCRC and oncocytomas are the most enhancing renal tumors, commonly with a maximal peak at the arterial or corticomedullary phase. Chromofobe renal cell carcinomas (ChRCC) and lipid-poor angiomyolipomas (AML) commonly show intermedium grade of enhancement (Fig. 7 on page 17).
The grade on enhancement can be visually assessed. A solid tumor enhancing to a clearly lower degree relative to renal cortex is suspicious of PRCC. Nevertheless, a quantitative evaluation is warranted. It can be based on the determination of maximal density, absolute enhancement, percentage of enhancement, and relative enhancement to renal cortex or to aorta in a region of interest with the visually estimated maximal attenuation. There is considerable overlapping in values obtained for different tumors, so that although many thresholds have been proposed, none can be considered absolute in the individual patient. The evaluation of voxel-based whole-lesion enhancement pattern has also been demonstrated as a valuable tool for distinguishing between CCRC and PRCC. A different pattern of voxel distribution is observed on whole-lesion histograms, with a tendency of CCRC to show higher interquartile range and standard deviation, and lower skewness and kurtosis (Fig. 8 on page 18).

PRCC not uncommonly shows cystic features. The solid areas of these partially cystic masses also enhance poorly, whereas solid components of cystic CCRC usually show intense contrast uptake that reflects the intense neoangiogenesis of these neoplasms. (Fig. 9 on page 18). Type 2 PRCC frequently present as cystic, usually large masses with internal necrosis and hemorrhage. There may be peripheral hypoenhancing papillary projections that are subtle on CT (Fig. 10 on page 19). Perirenal bleeding can also occur in type 2 high grade tumors, although it is exceptional (Fig. 11 on page 20).

Hyperdense renal cysts may be indistinguishable from PRCC on a monophasic CT examination. Some authors believe that type 1 PRCC might be an underdiagnosed condition owing to its indolent biologic behavior and the possibility of misinterpreting medium density renal focal lesions on contrast-enhanced CT as hemorrhagic cysts. Small percentages of CCRC enhance poorly and may mimic PRCC. Lymphoma, metastases and transitional cell carcinoma can also show discrete contrast enhancement (Fig. 12 on page 21).

Some investigations have found that basal hyperattenuation relative to renal parenchyma prior to contrast injection is characteristic of PRCC, which have a medium attenuation of 35 HU. Other authors state that it has no value for discriminating between PRCC and other renal neoplasms. It is also a typical feature of lipid-poor AML (Fig. 13 on page 22).

Calcifications are seen in 7-23 % of cases, with no added diagnostic value to distinguish from CCRC, although it allows discarding lymphoma (Fig. 14 on page 23). They can be peripheral and linear or rounded. Fat deposition secondary to bone metaplasia, massive necrosis and trapping of perirenal fat has also exceptionally been described.

There was venous involvement in 4% of cases in one series. PRCC approximately represent 8.5% of cases of RCC with extension to renal vein and inferior vena cava. This event is almost exclusively seen in type 2 tumors. Patients with renal cell carcinoma extending into the IVC with a papillary subtype show a considerably shorter survival
compared with those with a clear cell subtype. A patient with a PRCC extending into the IVC might be an inappropriate candidate for extensive surgery when metastases to nodes or distant organs are found. Tumoral thrombus secondary to PRCC shows poor enhancement, similarly to the primary tumor and contrary to other renal neoplasms with venous extension (Fig. 15 on page 23).

An infiltrating growing, extension to perirenal or sinusal fat and collecting system invasion (Fig. 16 on page 24) are rare features that are almost exclusively seen in cases of PRCC type 2 and also carry a bad prognosis.

Regional lymph node metastases are exceptional among type 1 tumors and are seen in approximately 15% of cases of type 2 PRCC. They use to share with the primary tumor the features of low-grade contrast uptake and cystic-hemorrhagic changes (Fig. 17 on page 25). Cystic changes can also be present, secondary to necrotic degeneration, in lymph nodes metastasis of CCRC.

The occurrence of distant metastases at diagnosis is only 1-3.7% in type 1 and 7.5-13% in type 2 PRCC. Metastases, as well as recurrent tumors, are usually hypoenhancing and can harbour cystic or hemorrhagic areas (Fig. 18 on page 26).

MAGNETIC RESONANCE IMAGING

MRI offers some advantages over CT in the characterization of PRCC.

Three patterns of presentation of PRCC at MRI have been described:

- A small peripheral T2-hypointense hypoenhancing solid mass (Fig. 19 on page 27). This pattern is the most common among type 1 tumors and seems to carry the best prognosis.
- A cystic lesion with hemorrhagic fluid and peripheral papillary projections (Fig. 20 on page 28). It is most frequent in type 2 tumors, representing an intermediate prognosis.
- A central, poorly circumscribed, infiltrative mass (Fig. 21 on page 29). This pattern has exclusively been described in a subset of type 2 PRCC with a poor prognosis.

Most (up to 89%) are hypointense on T2-weighted images compared to the renal parenchyma. This can be a differentiating feature from CCRC (Fig. 19 on page 27, Fig. 20 on page 28, Fig. 22 on page 29). Nevertheless, hyperintensity on T2 can also be seen in PRCC owing to edema and cystic-necrotic degeneration.

The tumor signal is variable on T1-weighted images. MRI easily depicts hemorrhage inside a cystic or necrotic lesion, which is a common feature of type 2 tumors (Fig. 17 on page 25, Fig. 20 on page 28, Fig. 21 on page 29).
47% had a lower in phase signal intensity than out of phase. This feature, which might be secondary to hemosiderin deposition, can be diffuse or focal and is rarely seen (9%) in CCRC.

The enhancement after Gadolinium-based contrast injection can be evaluated in terms of increase-in-signal percentage or as tumor-to-cortex index. PRCC are usually hypoenhancing tumors also on MRI if compared to CCRC (Fig. 19 on page 27, Fig. 20 on page 28, Fig. 21 on page 29, Fig. 22 on page 29). Nevertheless, MRI is more sensitive, and nearly all of the lesions, including those with no or minimal contrast uptake on CT, have a significant enhancement percentage. Subtraction images can help demonstrate subtle enhancement (Fig. 20 on page 28). The average contrast enhancement percentage, which is defined as significant over 15%, is 68%. The maximum enhancement is at the nephrographic phase, similar to what is found on CT.

The solid components of PRCC commonly show an intense restriction of water diffusion, with hyperintensity on DWI with a high b-value and low ADC (Fig. 19 on page 27, Fig. 20 on page 28, Fig. 21 on page 29). It is believed that this behavior might be partially owed to low perfusion. Some investigators suggest employing a biexponential model, applying multiple low b-values (intravoxel incoherent motion or IVIM) to discriminate between the perfusion fraction and tissue diffusivity that are contributing to the appearance on the monoexponential DWI model.

Infiltrative MRI appearance, which is present in approximately 7.8% of cases in one study, along with renal vein thrombus, which is seen in 89% of infiltrative cases, seems to identify a subset of pathological type 2 PRCC at a significantly increased risk of metastatic disease (Fig. 18 on page 26, Fig. 21 on page 29). This small fraction of cases exhibits a highly aggressive clinical course with a prognosis that is among the poorest of any subgroup of RCC. There might be an uninvestigated relationship between this radiological presentation and certain genetic subsets of type 2 tumors.

CCRC are usually heterogenous tumors with necrosis that show high signal on T2-weighted images. The solid components are also commonly hyperintense on T2, although to a lesser degree, and enhance intensely after Gadolinium injection, with an earlier peak. Despite higher histological and biological aggressiveness, they show higher ADC values. Lipid content in clear cytoplasm is responsible of a characteristic signal drop in out-of-phase T1-weighted images. If the signal intensity fall is superior to 25% and AML is discarded CCRC is very likely (Fig. 22 on page 29).

Lipid-poor AML shares some MRI features with focal PRCC. Both are frequently hypointense on T2 and show restricted water diffusion, with low ADC values. AML, however, commonly shows signal drop on out-of-phase T1 images, owing to microscopic fat (Fig. 23 on page 30).

ULTRASONOGRAPHY
Eighty three of RCC are detected on ultrasonography. The sonographic appearance has little value for discriminating among the histological subtypes of RCC. Moreover, 20-25% of RCC are hyperechogenic and 25% of AML are not.

Similarly to CT or MRI, US can depict cystic or necrotic components in an otherwise solid renal mass, or solid projections inside a cystic lesion.

Contrast enhanced ultrasound (CEUS) has proven superior to CT for demonstrating subtle enhancement by showing "bubbling" in cases of PRCC in which CT failed to clearly demonstrate contrast uptake (Fig. 24 on page 30).

CEUS is also sensitive for demonstrating contrast uptake in the papillary projections of a cystic-hemorrhagic mass, a feature that might be useful for lesion characterization. We have found some cases in which CEUS was more sensitive than MRI for this finding (Fig. 25 on page 31), but also one case in which it failed to demonstrate enhancement and MRI clearly depicted it (Fig. 21 on page 29).

**MULTIPLE AND HEREDITARY RPCC**

Two patients in our series had multiple, though to be sporadic, PRCC. In one case there were bilateral tumors (Fig. 26 on page 32).

There was one coexisting right-sided CCRC in the case of a 64 year-old man with a left-sided PRCC type 1 (Fig. 27 on page 32).

A 56 year-old man with multiple type 1 PRCC was classified as hereditary papillary renal carcinoma (HRPC) (Fig. 28 on page 33).

A 26 year-old woman with one type 2 PRCC was classified as hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome (Fig. 29 on page 34).

A 32 year-old woman with one type 1 PRCC was classified as papillary thyroid cancer-papillary renal neoplasm (Fig. 30 on page 35).
Fig. 4: Distribution of types of renal tumors in our series. PRCC constitutes the second most frequent pathologically proven renal tumor, with a percentage similar to previous reports.

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Fig. 5: Morphological usual features of non-fatty renal solid tumors. PRCC type 1 are homogeneous solid tumors. CCRC tend to be heterogeneous masses, with areas of necrosis when large. They can show infiltrative margins, although this is not a common feature. ChRCC are generally well defined expansive despite large size tumors, usually homogeneous except for an occasionally present central scar. Oncocytomas are commonly small round tumors with sharp margins. Lipid-poor AML do not show macroscopic fat and may exhibit intermediate contrast uptake.

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Fig. 6: Usual features of PRCC type 1 on multiphase CT. There is a small peripheral homogeneous solid renal tumor with low enhancement, which is maximal (40 HU) at the nephrographic phase.
Fig. 7: Findings at multiphase CT of other renal tumors. Clear cell carcinoma shows heterogeneous enhancement because of eccentric necrosis. The absolute enhancement is intense (139 HU) and maximal at the corticomedullary phase. Oncocytoma also enhance intensely (103 HU), with a subtle and characteristic reversal pattern at the late phase, optimally depicted with narrower window settings. Chromofobe carcinoma and fat-poor angiomyolipoma usually show medium enhancement, although in this particular case the chromofobe tumor enhances intensely (102 HU), reflecting individually overlapping features.

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**Fig. 8:** Discordant sporadic association of right CCRC and left PRCC. Value of whole-lesion voxel-attenuation evaluation. The distribution of voxel attenuation is different in whole-lesion evaluation, resulting, in a simplified form, in a wider, lower and right-sided histogram in the clear cell carcinoma. The differences in the graphics are attenuated because of different automatically applied scales.

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Fig. 9: Cystic lesions with solid projections. PRCC type 1 vs CCRC. The enhancement is much more intense in the CCRC (123 HU) relative to the PRCC (35 HU).

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**Fig. 10:** PRCC type 2. Cystic-hemorrhagic degeneration with subtle peripheral papillary projections. There is a right renal cystic mass with papillary projections that are overlooked with usual window setting for abdominal evaluation (upper row of images) and subtly depicted with narrow windows (middle row). They enhance between 11 and 15 HU (lower row), which is considered indeterminate.

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Fig. 11: PRCC type 2 with sarcomatoid features, showing perirenal spontaneous hemorrhage. There is a large cystic-hemorrhagic mass with peripheral papillary non-enhancing projections and perirenal high attenuation fluid. It proved to correspond to perinephric hemorrhage associated to a large PRCC type 2 with hemorrhagic degeneration and sarcomatoid features.

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Fig. 12: Renal tumors simulating PRCC on CT. Left side. Renal hemorrhagic cyst showing high basal attenuation (67 HU) and no enhancement (maximal increase in attenuation of 3 HU). If only a monophasic examination had been performed it would have been impossible to discern between dense renal cyst and type 1 PRCC. Middle. Poorly
enhancing (27 HU) CCRC. This feature is seen in a small percentage of CCRC. Right side. Renal metastasis from epidermoid lung carcinoma presenting as a predominantly necrotic renal mass that invades the collecting system, with peripheral solid components that show minimal contrast uptake, simulating type 2 PRCC. See also left pulmonary basal metastases with similar features.

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Fig. 13: Basal hyperattenuation. Upper and middle rows shows examples of tumors that are hyperdense relative to renal parenchyma on unenhanced images (PRCC type 1 and lipid-poor AML respectively). CCRC (lower row) are usually hypodense.
Fig. 14: Calcification in PRCC. CT shows a peripheral calcification in the component of a type 2 PRCC that is invading the renal collecting system (upper row). Calcification is a non-specific finding that is only rarely seen in PRCC and can also be found in other carcinoma subtypes, as CCRC (lower row). It allows discarding lymphoma.
Fig. 15: Different histologies of renal tumors with IVC extension. • Upper left. Papillary renal cell carcinoma. It is the second most common malignant neoplasm involving the kidney and showing venous extension. Both renal tumor and venous thrombus are hypoenhancing. • Upper right. Clear cell renal carcinoma. It is the most usual renal carcinoma and also the most frequently presenting with venous tumoral thrombosis (VTT). The thrombus, as well as the primary tumor, shows intense and heterogeneous contrast uptake. • Lower left. Renal leiomyosarcoma. The radiological appearance of both the primary tumor and the venous tumoral extension are indistinguishable from clear cell carcinoma. • Lower right. Sarcomatoid renal carcinoma. It also behaves similarly to clear cell carcinoma at imaging.

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Fig. 16: Type 2 PRCC infiltrating the renal collecting system. CT demonstrates invasion of the collecting system in two cases of patients presenting with gross hematuria. In the first case (left column, same patient as figure 14) there is dense content in the renal pelvis, demonstrated both in coronal (upper) and axial (lower) images, reflecting hemorrhagic content.

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Fig. 17: Lymph node metastases in type 2 PRCC. CT depicts regional lymphadenopathies in two cases of type 2 PRCC (left and middle columns). Renal primaries are cystic-hemorrhagic masses (*) with no (left) and midly enhancing (middle) papillary projections. T1-weighted image (middle low) demonstrates hemorrhagic content with high signal intensity. Lymph node metastasis (+) show similar imaging features as the primary malignancies. CCRC (right column) can also show similar findings owing to necrosis, although the solid components commonly show greater enhancement.

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**Fig. 18:** Local relapse and distal metastases in type 2 PRCC. CT performed prior to (upper left) and one year after nephrectomy (lower left) show a type 2 infiltrating PRCC (red *) with cystic-hemorrhagic features (yellow *), extension to renal vein (+) and a peripheral calcification (red arrow). One year after nephrectomy (lower left) there is hypoenhancing local relapse (blue *) and hypoenhancing liver metastases (yellow arrows). Metastases from CCRC (right column) are commonly hyperenhancing, maximally at the arterial phase (yellow arrow: adrenal metastasis; red arrows: contralateral renal metastases). There are central necrotic areas.

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**Fig. 19:** Typical MRI findings of type 1 PRCC as a focal solid homogeneous lesion. This peripheral mass exhibits low signal on T2-weighted image, slightly increase in signal in out-of-phase image and low ADC. There is mild enhancement of 87 %, maximal at the nephrographic phase.

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**Fig. 20:** Typical MRI findings of type 2 PRCC as a focal cystic-hemorrhagic lesion with papillary projections. The papillary projections were only subtly depicted on CT with narrow window settings. Neither CT or CEUS showed contrast uptake. MRI easily demonstrates these papillary projections in the periphery of a hemorrhagic (hyperintense on unenhanced T1-weighted image) lesion. They exhibit slight increase on signal on out-of-phase image, low ADC and mild late enhancement (17%), which is better appreciated.
on subtraction image and signal-to-intensity curve. Note how the hemorrhagic fluid appears bright on T2-weighted image in this case and the solid components are dark.

Fig. 21: Infiltrative growth pattern in type 2 PRCC with venous extension. Same patient as figure 18. There is an infiltrating tumor involving renal parenchyma with venous extension and cystic-hemorrhagic focal degeneration (high signal on T1). ADC values are low in the tumor and in the thrombus, and even lower in hemorrhage. The infiltrating tumor and the venous thrombus also show a similar pattern of enhancement, both at CEUS and MRI. The maximum enhancement is 84%.
**Fig. 22:** Typical MRI features of CCRC. There is a peripheral renal mass with necrotic areas. The solid components show high intensity on T2-weighted image, mild drop of its signal on out-of-phase image, and intermediate ADC values. There is intense enhancement (355%) peaking at the corticomedullary phase of the study. The necrotic areas show higher signal on T2, lower on T1 and high ADC, along with no significant enhancement.

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**Fig. 23:** Typical MRI features of lipid-poor AML. The lesion is hypointense on T2-weighted image and show low ADC values. The clues for excluding PRCC and suggesting AML are a signal drop of 18% on out-of-phase image and a relatively intense enhancement of 198% peaking at the corticomedullary phase.

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Fig. 24: CEUS demonstrating contrast uptake in type 1 PRCC. This peripheral small mass exhibits an equivocal enhancement of 15 HU on CT. Doppler ultrasound also fails to show vascularisation. CEUS demonstrates contrast uptake by depicting "bubbling" inside the lesion. Note in the video how the near cyst does not show any "bubbling".

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Fig. 25: CEUS clearly depicting enhancement of papillary projections in cystic-hemorrhagic type 2 PRCC. US shows a cystic peripheral small renal mass with echogenic papillary peripheral projections (arrows). CEUS easily demonstrates enhancement, whereas MRI hardly depicts enhancement even on subtracted images (not shown). Haemorrhage may contribute to obscure enhancement in small lesions.

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Fig. 26: Bilateral sporadic PRCC type 1 PRCC. 75 year-old male patient. Upper row: Current CT (left image) for active surveillance of two bilateral renal tumors (arrows) found on an examination performed three years earlier (middle image) for a different reason. Retrospectively reviewing another study that had been performed six years previously (right image), the left lesion was already present, with a lesser size. These slow-growing lesions are hypoenhancing with respect to renal parenchyma, with a maximal attenuation of less than 60 HU. The tumors are slightly hyperechogenic and hypovascular on ultrasonography. The patient finally decided to undergo biopsy of the left (most accessible) lesion, with a final diagnosis of PRCC type 1. He goes on active surveillance.

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Fig. 27: Discordant sporadic association of right CCRC and left type 1 PRCC. Same patient as figure 8. 64 year-old man. There is one small lesion in each of renal upper poles. The right one (red arrows) is slightly larger and shows more intense enhancement (mean attenuations of 36, 139, 112 and 87 HU at progressive phases of the study), some central low-density areas and discrete exophytic growth. The left lesion (blue arrows) is homogeneously hypoenhancing (30, 68, 62 and 51 HU). A hepatic hemangioma is incidentally found (yellow arrows). Histological analysis after partial bilateral nephrectomy confirmed the suspicion of right CCRC (with some central necrotic areas) and left PRCC type 1, both with a T1 stage.

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**Fig. 28:** Hereditary PRCC. Incidental sonographic finding of two renal masses. There is an exophytic cystic mass in the right kidney (red arrows). It contains a solid nodule (white arrow) that enhance to a lesser degree than the renal cortex. There is also a large left renal mass (*) with low somehow heterogeneous density. Biopsy immediately previous to radiofrequency ablation of the solid component of the right renal lesion revealed PRCC type 1. Left nephrectomy was performed three months later. The pathologist found a cystic hemorrhagic mass with solid papillae, with histological findings of PRCC type 1. There were also several renal milimetric adenomas.

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Fig. 29: Leyomyomatosis hereditary-renal cell carcinoma syndrome. 26 years-old woman. Same patient as figures 18 and 21. Large infiltrating left renal mass. There is a large area of cystic hemorrhagic degeneration (1) with papillary projections (2) and venous thrombus (3) almost reaching the inferior vena cava. The solid components of the mass enhance little. The hemorrhagic cystic content shows high signal intensity on T1-weighted image, heterogeneous signal with siderotic dark rim on T2 and very low ADC. The infiltrating component of the mass (4) is mildly hypointense on T2 and also has low ADC. The uterus is enlarged at the expense of multiple leiomyomata (*), some of them with ill-defined borders. One year after surgery a large local relapse mass (+) and distant hepatic low-enhancing metastases (arrows) have appeared.

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Fig. 30: Papillary Thyroid Cancer-Papillary Renal Neoplasm. 32 year-old woman who presents with lateral cervical lymphadenopathies. Cervical ultrasonography reveals an ill-defined nodular lesion in the left lobe of the thyroid gland (red arrows on the left), with microcalcifications. There are also left lymphadenopathies, that also contain microcalcifications and show high rigidity on qualitative strain elastography (white arrows on the right). CT confirms the findings (arrows). Abdominal CT also depicts a solid renal lesion that appears as slightly hyperdense on non-contrast phase and shows only mild enhancement at nephrographic and late phases. CEUS was performed for distinguishing between mild enhancement of a solid mass and pseudoenhancement of a cystic dense lesion, confirming enhancement (*). Histological analysis after surgeries proved papillary thyroid carcinoma and PRCC.

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Conclusion

- PRCC are probably underdiagnosed. Radiologists should be familiarized with some imaging features that can lead to the best management of patients.
- Solid components of PRCC enhance poorly. Type 1 PRCC are usually small homogenously hypodense sharply delineated tumors.
- Cystic and hemorrhagic degeneration, perinephric or sinusal fat and collecting system invasion, extension to renal or inferior cava veins, infiltrating growing, nodal involvement, metastasis, and recurrence are more frequent in type 2 tumours. Tumors with these findings carry a worse prognosis.
- CEUS is helpful for depicting subtle enhancement, both in solid homogeneous type 1 tumors and in papillary projections of necrotic and hemorrhagic type 2 PRCC.
- MRI is useful in depicting mural nodules inside cystic lesions, hemorrhage and subtle enhancement. Hypointensitiy on T2 weighted-images, low ADC and absence of signal drop in out-of-phase images are characteristic findings of PRCC.
- Dense cysts and lipid-poor angiomyolipomas, among other conditions, can mimic some features of PRCC.
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