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Epidemiology, pathology, and pathogenesis of renal cell carcinoma

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INTRODUCTION

Renal cell carcinomas (RCCs), which originate within the renal cortex, are responsible for 80 to 85 percent of all primary renal neoplasms. Transitional cell carcinomas of the renal pelvis are the next most common (approximately 8 percent). Other parenchymal epithelial tumors, such as oncocytomas, collecting duct tumors, and renal sarcomas, occur infrequently. Nephroblastoma or Wilms tumor is common in children (5 to 6 percent of all primary renal tumors), while renal medullary carcinoma is a rare form of RCC seen in sickle cell disease and sickle cell trait. (See "Presentation, diagnosis, and staging of Wilms tumor" and "Sickle cell disease effects on the kidney".)

The epidemiology, pathology, and pathogenesis of RCC will be reviewed here. The clinical and radiographic presentation, staging methods, prognosis, and management of these tumors are discussed separately. (See "Clinical manifestations, evaluation, and staging of renal cell carcinoma" and "Prognostic factors in patients with renal cell carcinoma" and "Overview of the treatment of renal cell carcinoma" and "Definitive surgical management of renal cell carcinoma" and "Systemic therapy of advanced clear cell renal carcinoma" and "Antiangiogenic and molecularly targeted therapy for advanced or metastatic clear cell renal carcinoma" and "The treatment of advanced non-clear cell renal carcinoma".)

EPIDEMIOLOGY

Incidence — Globally, the incidence of renal cell carcinoma (RCC) varies widely from region to region [1], with the highest rates observed in the Czech Republic and North America [2]. In the United States, there are approximately 80,000 new cases and almost 14,000 deaths from RCC each year [3]. Worldwide, there are over 400,000 new cases of RCC and over 170,000 deaths annually due to kidney cancer [4].

Sex and age — RCC is approximately twofold more common in males compared with females [3]. RCC occurs predominantly in the sixth to eighth decade of life with median age at diagnosis around 64 years of age; it is unusual in patients under 40 years of age and rare in children [5-7].

Ethnicity — Within the United States, Asian American patients or patients of Pacific Islander descent have the lowest incidence of renal cancers, compared with patients of other ethnicities [3]. The five-year survival rate for African American patients is similar to that for White American patients (approximately 75 percent) [3].

Extent of disease — Data from the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) registry covering 2009 through 2015 show the extent of disease at presentation of patients with RCC [8]:

- Localized disease (ie, confined to the kidney): 65 percent
- Regional disease (ie, spread to regional lymph nodes): 17 percent
- Metastatic disease: 16 percent
- Unstaged: 3 percent

In an analysis of over 29,000 cases from the SEER registry, there has been a steady decrease in the size of tumors at presentation [9]. This is likely due to the greater number of incidental tumors detected on abdominal imaging. For example, data from the National Cancer Database showed that the size of stage I tumors decreased from a mean of 4.1 cm in 1993 to 3.6 cm in 2003 [9]. Whether all of the asymptomatic RCCs diagnosed through improved imaging are clinically relevant is uncertain [10].

Mortality — The five-year survival rate of patients with kidney cancer has doubled over the last 60 years, from 34 percent in 1954 to 62 percent in 1996 and 75 percent from 2009 to 2015 [8,11]. The incidence of RCC has risen more than threefold higher than the mortality rate [3]. This improved survival and case-fatality rate is mostly due to earlier detection of these tumors at smaller sizes (ie, <4 cm) and curative surgical treatment [10].

ESTABLISHED RISK FACTORS

Smoking — Cigarette smoking is associated with an increased risk of developing renal cell carcinoma (RCC). In a meta-analysis that included data from 24 studies, the relative risks for RCC for all smokers, current smokers, and former smokers were 1.31, 1.36, and 1.16, respectively [12]. Furthermore, increasing use of cigarettes appears to be associated with more advanced disease (pathologic T3, lymph node involvement, or metastatic disease) at presentation [13].

Hypertension — Hypertension predisposes to RCC development [14], which seems to be independent of antihypertensive medications or obesity. The independent contribution of both has been difficult to sort out due to their close correlation with hypertension itself [15]. The underlying biological explanations linking hypertension to RCC remain largely unknown [16-20].

Obesity — Excessive body weight is a risk factor for RCC in both males and females [21,22]. This was shown in a prospective analysis of over 300,000 participants in the National Institutes of Health and American Association for Retired Persons (NIH-AARP) Diet and Health Study [22]. The relative risk (RR) of RCC increased progressively with baseline body mass index (BMI).

For patients with newly diagnosed RCC, excess body weight is associated with a lower stage and lower grade disease [23]. Furthermore, in patients with metastatic disease, RCC is associated with a longer overall survival for those with excess body weight compared with those with normal or below normal body weight [24-26]. The improved prognosis in these patients may be associated with decreased expression of the fatty acid synthase (*FASN*) gene.

Acquired cystic disease of the kidney and chronic kidney disease — The risk of developing RCC has been estimated to be up to 30 times greater in dialysis patients with acquired polycystic disease of the kidney than in the general population [27]. Among chronic dialysis patients, the incidence of acquired cystic disease is approximately 35 to 50 percent, and approximately 6 percent of these patients eventually develop RCC [28]. Even among patients with chronic kidney disease who are not dialysis dependent, a decreasing estimated glomerular filtration rate (eGFR) is associated with an increased risk of kidney cancer [29]. (See "Acquired cystic disease of the kidney in adults".)

Occupational exposure — Occupational exposure to toxic compounds, such as cadmium, asbestos, and petroleum byproducts, has been associated with an increased risk of RCC [30-32]. In one international multicenter study of over 1700 patients with RCCs and 2300 controls, an increased risk of cancer was observed in those exposed to asbestos (RR 1.4, 95% CI 1.1-1.8), cadmium (RR 2.0, 95% CI 1.0-3.9), and gasoline (RR 1.6, 95% CI 1.2-2.0) [30]. Cadmium workers who smoke may have a particularly high incidence of RCC [33]. Studies of occupational exposures are often limited by the lack of specific exposure details. Increased exposure to such carcinogens may be associated with pathogenic variants in genes associated with the

pathogenesis of RCC, such as the von Hippel-Lindau (*VHL*) tumor suppressor gene. (See "Molecular biology and pathogenesis of von Hippel-Lindau disease".)

The relationship between pathogenic variants in this gene and exposure to trichloroethylene, a petroleum byproduct used as a metal degreaser, was evaluated in 44 patients with RCC and known exposure to the toxin, 107 with RCC but no known exposure, and 97 healthy controls [34]. A specific mutational hot spot in the *VHL* gene was found in 39 percent of those with toxin exposure, but not in any of those without exposure nor in any of the healthy individuals. Although these data are intriguing and suggest a link among carcinogen exposure, genetic damage in a specific site, and renal cancer, it does not prove causation.

Analgesics — The prolonged ingestion of analgesic combinations, particularly compounds containing phenacetin (of which acetaminophen is a major metabolite) and aspirin, can lead to chronic renal failure. Such patients are at increased risk for renal pelvic and urothelial tumors.

Epidemiologic studies have demonstrated an increased risk for RCC with heavy use of aspirin, nonsteroidal antiinflammatory drugs (NSAIDS), and acetaminophen, although the risk may vary depending on the agent [35,36]. (See "Urinary tract malignancy and atherosclerotic disease in patients with chronic analgesic abuse" and "Malignancies of the renal pelvis and ureter".)

- In one of the largest prospective studies that included data from 77,525 females followed over 16 years and 49,043 males followed over 20 years, the risk of developing RCC appeared to vary by agent, and the regular use of aspirin or acetaminophen was not associated with the development of RCC [36]. By contrast, the routine use of nonaspirin NSAIDs was associated with a greater risk of RCC (hazard ratio [HR] 1.51, 95% CI 1.12-2.04), which increased with more frequent use and longer period of use.

- By contrast, data from 1217 RCC cases and 1235 controls in the United States Kidney Cancer Study, and 98,807 participants in the United States Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) found that nonprescription acetaminophen use, but not that of aspirin or NSAIDs, increased the risk of developing RCC [37].

Genetic factors — The risk of a second, metachronous RCC is increased in patients who have been treated for one renal cancer. This increased risk is most pronounced with younger age at the first RCC, suggesting that early onset renal cancer has a genetic component [38].

Although most RCCs are sporadic, several syndromes associated with RCC have been described. Factors that favor a hereditary contribution in patients without a clear genetic disease include first degree relatives with a tumor, onset before the age of 40, and bilateral or multifocal disease [39]. Other individuals with a clear genetic contribution have abnormalities on

chromosome 3 [40-44], and additional genetic abnormalities have been identified in other families [45-47], suggesting that these tumors represent distinct disease entities.

Patients with inherited polycystic disease may have an increased risk of RCC (as well as liver and colon cancer), even in the absence of kidney dysfunction or end-stage kidney failure. One cohort study from Taiwan observed that the risk of RCC was increased in such patients with inherited polycystic kidney disease compared with a matched control group (adjusted HR 2.5, 95% CI 1.3-4.7) [48]. In inherited polycystic kidney disease, the kidney tumors are more often bilateral at presentation (12 versus 1 to 4 percent in sporadic RCC in the general population), multicentric (28 versus 6 percent), and harbor sarcomatoid features (33 versus 1 to 5 percent) in type [49,50]. (See "Autosomal dominant polycystic kidney disease (ADPKD): Kidney manifestations", section on 'Renal cancer'.)

Specific inherited syndromes associated with RCC are discussed separately. (See "Hereditary kidney cancer syndromes".)

Cytotoxic chemotherapy — The use of cytotoxic chemotherapy in childhood for malignancies, autoimmune disorders, or bone marrow transplant conditioning has been associated with the subsequent development of translocation RCC [51]. (See 'Translocation renal cell carcinoma (MiT/TFE-related RCC)' below.)

Chronic hepatitis C infection — An epidemiologic study of over 67,000 patients found that chronic infection with hepatitis C virus was associated with a significantly increased risk of RCC after correcting for age, ethnicity, sex, and the presence of chronic kidney disease (HR 1.77, 95% CI 1.05-2.98) [52]. (See "Overview of kidney disease associated with hepatitis C virus infection".)

Sickle cell disease — Patients with sickle cell trait and (to a lesser extent) sickle cell disease are at risk for renal medullary carcinoma. Further data are discussed separately. (See "Sickle cell disease effects on the kidney", section on 'Renal medullary carcinoma'.)

Kidney stones — A history of kidney stones may be associated with both RCC and transitional cell carcinoma of the upper urinary tract [53]. In a meta-analysis that pooled data from almost 63,000 patients with kidney stones, the risk ratio of developing RCC was 1.96 (95% CI 1.24-2.49), and the increased risk appeared to be largely limited to males. The risk ratio for transitional cell carcinoma was 2.14 (95% CI 1.35-3.40). However, the study is subject to a number of limitations, including recall/reporting bias and the increased frequency of scans in patients with stones.

OTHER FACTORS THAT MODIFY RISK

Diabetes mellitus — A history of diabetes mellitus has been associated with a modest increase in the risk of renal cell carcinoma (RCC) in some studies but not in others [54-57]. This may be mediated through an increase in the incidence of hypertension and obesity [57].

Alcohol — Alcohol intake is associated with a protective effect on the risk of RCC in both males and females [58-61]. However, this should not be viewed as a reason to begin drinking alcohol. A topic on the risks and benefits of alcohol consumption is covered separately. (See "Overview of the risks and benefits of alcohol consumption".)

The protective effect of alcohol on the risk of RCC was shown in a 2012 meta-analysis of 20 studies [60]. Alcohol consumption was associated with a lower risk of developing RCC compared with no alcohol consumption (relative risk [RR] 0.85, 95% CI 0.80-0.92) [60]. The reduction in risk was seen with light (0.01 to 12.49 g/day) and moderate (12.5 to 49.9 g/day) alcohol consumption, and was not altered after adjustment for smoking, body mass index (BMI), or a history of hypertension.

Other factors — Additional clinical factors that may increase the risk of developing RCC include dietary factors such as the intake of nitrite from processed meat sources [62], reproductive factors (eg, increasing number of pregnancies), and prior radiation therapy (RT) [63-65]. For females, the use of oral contraceptives may reduce risk [63,64].

Childhood cancer survivors — At least one study suggests that childhood cancer survivors are at an increased risk for RCC, particularly if they were previously treated with RT directed at the kidney or with cisplatin [66].

In a report from the Childhood Cancer Survivor Study that followed over 14,000 survivors for a median follow-up of 24 years, survivors were more likely to develop renal carcinoma compared with the general population (standardized incidence ratio 8.0, 95% CI 5.2-11.7). However, the overall incidence of RCC was low (26 cases detected during follow-up). On multivariate analysis, significant risk factors for RCC were prior treatment with radiation of 5 Gy or greater directed to the kidney (RR 3.8, 95% CI 1.6-9.3) and cisplatin exposure (RR 3.5, 95% CI 1.0-11.2).

PATHOLOGY

Although lesions smaller than 3 cm were previously thought to represent benign adenomas, it is now clear that even small tumors can represent carcinomas [67,68]. As a result, the distinction between a malignant and a benign growth based on size alone may not be sufficient. Instead, basic histologic criteria are used to discriminate between a malignant or benign growth. (See "Diagnostic approach, differential diagnosis, and management of a small renal mass".)

Renal cell carcinomas (RCCs) were initially classified by cell type and growth pattern [69]. This classification has evolved to more accurately reflect the morphology, growth pattern, cell of origin, histochemical, and molecular basis of the different types of adenocarcinomas [70-73]. The impact of pathology on prognosis is discussed separately. (See "Prognostic factors in patients with renal cell carcinoma", section on 'Histopathology'.)

Several distinct subtypes of RCC have been identified, including the following:

- Clear cell (75 to 85 percent of tumors) – (see 'Clear cell carcinomas' below)
- Papillary (10 to 15 percent) – (see 'Papillary carcinomas' below)
- Chromophobe (5 to 10 percent) – (see 'Chromophobe carcinomas' below)
- Oncocytic (3 to 7 percent) – (see 'Oncocytomas' below)
- Collecting duct (very rare) – (see 'Collecting duct tumors' below)
- Molecularly defined renal cell carcinomas (rare) – (see 'Molecularly defined renal cell carcinomas' below)

Up to 5 percent of RCCs are considered unclassified. In two reports, these tumors had a worse prognosis compared with clear cell cancers [74,75], although another report found that the outcome was not different after adjusting for adverse clinicopathologic features such as stage and grade [76]. (See "The treatment of advanced non-clear cell renal carcinoma", section on 'Unclassified renal cell carcinoma'.)

RCC with sarcomatoid features is not considered a distinct subtype because sarcomatoid dedifferentiation can be seen in any histologic subtype of RCC. (See 'Renal cell carcinoma with sarcomatoid features' below and "Renal cell carcinoma with sarcomatoid features", section on 'Epidemiology'.)

Clear cell carcinomas — Clear cell carcinomas, which typically have a deletion of chromosome 3p, arise from the proximal tubule [77,78]. Macroscopically, they may be solid or less commonly, cystic. In addition to occurring in sporadic disease, clear cell carcinomas are specifically associated with von Hippel-Lindau (VHL) disease. (See "Clinical features, diagnosis, and management of von Hippel-Lindau disease".)

A poor prognosis is associated with higher nuclear grade or the presence of a sarcomatoid pattern (particularly with early stage disease) [79-81].

On the other hand, a more favorable prognosis has been associated with the rare multilocular variant of cystic clear cell RCC compared with other clear cell carcinomas [82-85].

Genomic alterations in clear cell carcinoma — Because clear cell carcinoma is the most common subtype of RCC, much work has been done to classify these cancers based on genetic alterations [86].

Chromosomal-level alterations — Common chromosome-level alterations in sporadic clear cell RCC include the following [87]:

- Loss of 3p (91 to 94 percent), which contains several genes associated with RCC, including the VHL, BRCA1 associated protein 1 (BAP-1), and protein polybromo 1 (PBRM1) genes, among others (see 'Von Hippel-Lindau gene' below and 'PBRM1 gene' below)
- Gain of 5q (67 to 69 percent)
- Monosomy or partial loss of 14q (42 to 45 percent)
- 7q gain (20 percent)
- 8p deletion (32 percent)
- 9p loss (29 percent)

Several specific gene and pathway alterations described in RCC are discussed below:

Von Hippel-Lindau gene — The *VHL* gene is found on chromosome 3 (3p25 to 26). Abnormalities in the *VHL* tumor suppressor gene are implicated in most cases of clear cell RCC (both sporadic and familial [ie, due to VHL disease]) [88-90]. In patients with sporadic RCC, somatic pathogenic variants or promoter hypermethylation in the *VHL* gene are observed in a majority (eg, 58 to 91 percent) of cases [86,88,90,91]. (See "Molecular biology and pathogenesis of von Hippel-Lindau disease" and "Clinical features, diagnosis, and management of von Hippel-Lindau disease", section on 'VHL somatic pathogenic variants in sporadic tumors'.)

PBRM1 gene — The switch/sucrose nonfermentable (SWI/SNF) chromatin remodeling complex gene protein polybromo 1 (*PBRM1*) has been found to be a second major clear cell RCC gene, with pathogenic variants in 33 to 41 percent of cases. Interestingly, *PBRM1* maps to chromosome 3p21 and is a tumor-suppressor gene [86,91,92].

BAP1 gene — The *BRCA1* associated protein 1 (*BAP1*), located at 3p, is mutated in 10 to 19 percent of clear cell RCC and encodes a nuclear deubiquitinase [86,91,93]. It is part of the large ubiquitin-mediated proteolysis pathway (UMPP). *BAP1*-mutant tumors are more likely to be aggressive and display adverse pathologic features, leading to worse survival [94,95]. (See 'Ubiquitin-mediated proteolysis pathway' below.)

Inactivation of histone-modifying genes — Inactivating pathogenic variants in two genes encoding enzymes involved in histone modification have been identified in RCC, including the SET domain containing protein 2 (*SETD2*) and the Jumonji AT-rich interactive domain 1C (*JARID1C*) [86,91,96]. These findings highlight that the chromatic modification machinery may be important to the pathogenesis of RCC.

Ubiquitin-mediated proteolysis pathway — UMPP is an important pathway for protein degradation through the proteasome. Alterations in UMPP result in similar functional consequences (ie, hypoxia) as *VHL* inactivation [97]. In one study, UMPP was the most frequently altered pathway in clear cell RCC [97]. Of note, the *VHL* and *BAP1* genes are members of this pathway.

Abnormalities in cellular division — The development of RCCs may also involve abnormalities in genes that control cell division. These include the Ras family genes and the *TP53* tumor suppressor gene. Although pathogenic variants in the *TP53* gene are identified infrequently in RCCs [98], overexpression of p53 protein is detected in approximately one-half of tumors [98]. Overexpression of p53 may be associated with more aggressive behavior and a worse prognosis [98,99]. This was illustrated by a series of 175 patients, in which the ten-year disease-specific survival was lower for patients whose tumors stained for p53 (48 versus 78 percent, compared with those not overexpressing p53) [98].

As part of The Cancer Genome Atlas (TCGA) project, more than 400 clear cell RCC tumors were surveyed using different genomic platforms. Alterations in genes controlling cellular oxygen sensing such as *VHL* were common. The phosphatidylinositol-4, 5-bisphosphate 3-kinase, protein-kinase B (PI(3)K/AKT) pathway was recurrently mutated, as well as the SWI/SNF chromatin remodeling complex (that includes *PBRM1*, *ARID1A*, *SMARCA4*). In addition, aggressive cancers demonstrated evidence of a metabolic shift involving downregulation of genes involved in the tricarboxylic acid (TCA) cycle and upregulation of the pentose phosphate pathway [86].

Renal cell carcinoma with sarcomatoid features — Sarcomatoid dedifferentiation, the most common form of tumor dedifferentiation, consists of cell components that are spindled or otherwise resemble sarcoma cells [100-102]. However, RCC with sarcomatoid features (ie, sarcomatoid RCC) is not classified as a distinct tumor subtype because it can be seen in any histologic subtype of RCC, at varying frequencies [100,101]. (See "Renal cell carcinoma with sarcomatoid features", section on 'Epidemiology'.)

Histology — The diagnosis of sarcomatoid RCC is based on the presence of sarcoma-like cells, with no minimum amount of cells with sarcomatoid appearance needed to establish the diagnosis [100,101]. The sarcomatoid cells most often resemble fibrosarcoma (sheets of

whorled spindle cells) or fibrous histiocytoma (spindle cells in a storiform pattern) [100] but can also include chondroid or osteoid differentiation [103-105]. The cells are often pleomorphic and present a high degree of nuclear atypia. RCC tumors with any sarcomatoid component are categorized as grade IV by convention [100-102].

The abundance of sarcomatoid features within a tumor can vary between 1 and 100 percent, with a median of 40 to 50 percent [106,107]. Tumors that are entirely composed of sarcomatoid features and where no epithelioid component can be identified are termed unclassified RCC [100,101]. The proportion of sarcomatoid features within a tumor has been suggested to be a prognostic factor, with a higher proportion associated with worse prognosis [106]. However, no uniform cut-off of the proportion of sarcomatoid features has been validated as a prognostic variable (10, 20, 25, 50, and 75 percent have all been proposed) [106-109]. Additionally, studies have not demonstrated an association between the proportion of sarcomatoid features and prognosis, after adjusting for confounding factors [106,107]. (See 'Pathology' above.)

Multiple other features of aggressive disease often occur concurrently with sarcomatoid features in RCC. Necrosis occurs in 90 percent of sarcomatoid RCC tumors [106] and microvascular invasion in 30 percent of cases [110]. Rhabdoid features (the second most common form of dedifferentiation in RCC, which is characterized by large eosinophilic cells with large eccentric nuclei) simultaneously occurs in approximately 25 percent of sarcomatoid RCCs [111]. The co-occurrence of these features does not appear to be associated with different tumor biology or disease course [111].

Molecular alterations — The study of the molecular features of sarcomatoid tumors have also yielded clinically relevant insights. The paired characterization of the sarcomatoid and epithelioid components of sarcomatoid tumors has shown that the molecular profiles and X-inactivation patterns of the two components are largely similar [112,113]. These findings have suggested that the two components originate from a common epithelial clonal origin, disproving a previously long-held hypothesis that these tumors could be sarcomas or carcinosarcomas. RNA-sequencing analyses have also shown that the molecular profiles of these tumors largely follow that of the background epithelioid histology [114]. However, multiple molecular alterations have been suggested to be specific to sarcomatoid RCC tumors. *NF2* [111,115] and *BAP1* [111,114] pathogenic variants, *CDKN2A* deletions [111,116], and *EZH2* amplifications [111] all appear to be enriched in sarcomatoid RCC tumors. While these molecular alterations are potential targets for systemic therapies, further studies are necessary to determine if they are clinically actionable.

Patients with sarcomatoid RCC often have rapidly progressive disease that is less responsive to antiangiogenic therapies. Molecular analyses of sarcomatoid tumors suggest that specific

molecular alterations differentiate them from nonsarcomatoid tumors and may underlie their robust responses to checkpoint inhibitor immunotherapy. In particular, sarcomatoid RCC tumors are enriched in *CD274* (programmed cell death ligand 1 [PD-L1] gene) amplifications [117,118], have higher PD-L1 protein expression on tumor cells [111,116,119,120], greater tumor infiltration by CD8+ T cells [111,120], and increased expression of interferon-gamma response and antigen presentation machinery genes [111,116]. While these features may explain the increased responsiveness of these tumors to immune checkpoint inhibitors, none serve as biomarkers in clinical practice.

Further details on the clinical presentation and management of RCC with sarcomatoid features are discussed separately. (See "Renal cell carcinoma with sarcomatoid features".)

Papillary carcinomas — Papillary RCC accounts for approximately 15 percent of all kidney cancers. As with clear cell cancers, papillary RCC originates from the proximal tubule [77,78], but these tumors are morphologically and genetically distinct malignancies. The molecular pathogenesis of papillary RCC was initially described in patients with hereditary forms of RCC. (See "Hereditary kidney cancer syndromes".)

Historically, papillary RCC has been classified as type I or type II, mostly based on cytopathologic findings [121]. Alternatively, papillary RCC can be classified by *MET* status *(MET*-driven versus not) [122] and by morphology (biphasic, Warthin-like, solid, papillary renal neoplasm with reverse polarity). Initial studies show that classification by morphology may correlate with distinct genomic features [101,102].

Classification of papillary RCC into types 1 and 2 is not used in the 2022 WHO classification of renal tumors [102]. This is primarily because of the classification's poor inter-operator reliability, as some papillary tumors have features of both subtypes or are classified as neither. Many type 2 papillary RCCs have also been reclassified as other molecularly driven subtypes, such as fumarate hydratase (FH) deficient RCC [101,102]. However, this classification remains widely used and is therefore still referenced here.

- **Type 1 papillary RCC** – Type 1 papillary RCC typically presents with stage I or II disease, and these patients have a relatively favorable prognosis. Although type 1 lesions occur in patients with hereditary papillary RCC, the majority of these are sporadic. In the hereditary form of this disease, activating germline pathogenic variants are seen in *MET*. In nonhereditary forms of the disease, somatic pathogenic variants in *MET* have been identified in approximately 10 to 20 percent of cases [121,123]. In total, altered *MET* status (defined as pathogenic variant, splice variant, or gene fusion) or increased chromosome 7 copy number (which encodes *MET* but may also involve other genes) was identified in 81

percent of type 1 papillary RCCs. One study in patients with advanced papillary RCC proposed a biomarker-driven classification of papillary RCC based on the presence of *MET* pathogenic variants [124].

- **Type 2 papillary RCC** – Type 2 papillary RCC is frequently associated with an aggressive course and advanced stage at presentation and is associated with a poor prognosis. Many tumors that used to be categorized as type 2 papillary RCC (based on morphology) have been reclassified into other molecularly defined subtypes of RCC. These tumors are less likely to have alterations in the *MET* pathway [124]. (See 'Molecularly defined renal cell carcinomas' below.)

The treatment approach to patients with papillary RCC is discussed separately. (See "The treatment of advanced non-clear cell renal carcinoma", section on 'Papillary renal cell carcinoma'.)

Chromophobe carcinomas — Histologically, chromophobe carcinomas are composed of sheets of cells that are darker than clear cell carcinoma. They lack the abundant lipid and glycogen that is characteristic of most RCCs, and originate from the intercalated cells of the collecting system [125-127].

Chromophobe carcinomas have a hypodiploid number of chromosomes, but have not deleted the 3p chromosomal genetic locus [128,129]. One study using comparative genomic hybridization found that 17 of 19 tumors exhibited a wide variety of abnormalities, including various combinations of the loss of chromosomes 1, 2, 6, 10, 13, 17, or 21 [129]. In a study of gene expression profiling in RCC, the *KIT* oncogene was found to be upregulated specifically on the cell membranes of chromophobe RCC [130].

Chromophobe carcinomas may have a lower risk of disease progression and death compared with clear cell carcinomas, although this is likely due to the fact that patients present at a lower stage [131-134]. This is illustrated in the following series:

- In a series that included 392 patients, the recurrence rate was 9 percent and the cancer-related mortality rate was 6 percent at a median follow-up of 44 months [132]. Significant prognostic factors for cancer-specific survival were sex, disease stage, and the presence of sarcomatoid differentiation.

- In another series of 124 patients seen at two institutions, the five-year disease-specific survival was better than with clear cell carcinoma (78 versus 60 percent) [131]. However, when corrected for stage, this survival difference disappeared.

As part of the TCGA project for chromophobe RCCs, 66 chromophobe RCCs were analyzed. Mitochondrial DNA and gene expression analysis suggested mitochondrial function as an important component of the disease biology. Genomic rearrangements showed recurrent structural breakpoints within the telomerase reverse transcriptase (TERT) promoter region, which correlates with highly elevated TERT expression [135].

The treatment approach to patients with chromophobe carcinomas is discussed separately. (See "The treatment of advanced non-clear cell renal carcinoma", section on 'Chromophobe renal cell carcinoma'.)

Oncocytomas — Renal oncocytomas are uncommon and consist of a pure population of oncocytes, which are large well-differentiated neoplastic cells with intensely eosinophilic granular cytoplasm that is due to a large number of mitochondria [136-138]. They account for approximately 3 to 7 percent of all renal tumors [139]. Like chromophobe carcinomas, oncocytomas appear to originate from the intercalated cells of the collecting ducts [139]. While sporadic oncocytomas are usually unilateral and single, multiple and bilateral oncocytomas have been described in patients with tuberous sclerosis complex (TSC) and Birt-Hogg-Dubé syndrome [140,141]. (See "Renal manifestations of tuberous sclerosis complex", section on 'Oncocytoma' and "Hereditary kidney cancer syndromes", section on 'Birt-Hogg-Dubé syndrome' and "Renal manifestations of tuberous sclerosis complex".)

Distinguishing an oncocytoma from an RCC histologically can occasionally be difficult. In one study, approximately 5 percent of solid tumors previously thought to be RCCs may have been oncocytomas [136]. Early reports of "metastatic oncocytomas" probably represented chromophobe RCCs [142]. (See 'Chromophobe carcinomas' above.)

The heterogeneity of renal oncocytomas has been seen in chromosomal analyses of renal oncocytomas, including combined loss of chromosomes Y and 1, rearrangements involving the cyclin D1 (*CCND1*) locus located at chromosome 11q13, involvement of 12q12-13, and loss of 14q [139]. This information has been proposed as a means of distinguishing oncocytoma from chromophobe RCC [143,144]. In one study, none of 36 chromophobe RCCs expressed cyclin D1 (measured by immunohistochemistry) or had a *CCND1* rearrangement; however, 21 of 63 (33 percent) oncocytomas showed cyclin D1 overexpression, and 12 of these (57 percent) were positive for a *CCND1* rearrangement [144].

Renal oncocytomas almost invariably behave in a benign fashion, despite the recognition that the growth rate could be similar to RCC. Even when very large, they are generally well encapsulated and are rarely invasive or associated with metastases [145,146].

A coexisting RCC can be identified in 10 to 32 percent of patients with oncocytoma, especially in those patients presenting with diffuse oncocytic nodules involving the renal parenchyma (also known as renal oncocytosis) [142,147,148]. Thus, patients with oncocytomas should be closely monitored and treated if there is evidence of rapid growth of the renal tumor.

Despite the high frequency of coexisting RCCs, the risk of metachronous renal tumors after resection of an oncocytoma is low. In a retrospective single-institution series of 424 patients who were followed for a median of seven years after radical or partial nephrectomy, 17 subsequent renal tumors (4 percent) were identified at a median of three years after the original diagnosis [149]. Of these, eight were oncocytomas, four were RCCs, and no pathology was available on the other five.

Collecting duct tumors — Although collecting duct (Bellini duct) tumors are rare, they tend to occur in younger patients and are frequently aggressive [150,151]. They commonly present with gross hematuria.

The largest reported series comes from the Surveillance, Epidemiology and End Results (SEER) database, which identified 160 cases that were compared with 33,000 cases of clear cell carcinoma identified during the same period [150]. Collecting duct carcinomas occurred at a younger age, were more frequent in Black individuals, and more commonly presented with advanced (T3/T4) or metastatic disease. On multivariate analysis, there was a significant increase in risk of death after correcting for stage and grade compared with clear cell carcinoma (hazard ratio [HR] 2.4).

Collecting duct tumors have not been associated with a consistent pattern of genetic abnormalities. Biologically, these tumors more closely resemble transitional cell than RCCs [152]. One report of 17 cases assessed by comprehensive genomic profiling showed *NF2* and *CDKN2A* alterations in 29 and 12 percent, respectively [153].

The treatment approach to patients with collecting duct tumors is discussed separately. (See "The treatment of advanced non-clear cell renal carcinoma", section on 'Collecting duct and renal medullary carcinoma'.)

Molecularly defined renal cell carcinomas — While the diagnosis and treatment of RCC mostly relies on histopathology, some RCC subtypes are defined by characteristic molecular features.

Fumarate hydratase-deficient RCC and hereditary leiomyomatosis and renal cell cancer associated RCC — Fumarate hydratase-deficient renal cell carcinoma (RCC) is characterized by biallelic loss of the fumarate hydratase (*FH*) gene that are either sporadic (ie, due to a somatic

pathogenic variant) or inherited (ie, due to a germline pathogenic variant) [154]. The *FH* gene encodes fumarate hydratase, a crucial enzyme in the tricarboxylic acid (TCA) cycle. Patients with germline pathogenic variants in *FH* present with hereditary leiomyomatosis and renal cell cancer syndrome (HLRCC). (See "Hereditary kidney cancer syndromes", section on 'Hereditary leiomyomatosis and renal cell cancer syndrome'.)

FH-deficient renal cell carcinomas are aggressive tumors and are associated with activation of the NRF2-antioxidant response element (ARE) pathway [155,156]. These tumors have relatively low tumor mutational burden compared with clear cell renal RCC but have a higher burden of copy number alterations, have CpG island hypermethylation, and are enriched in *NF2* pathogenic variants [154,157].

The treatment of patients with FH-deficient RCC and HLRCC is discussed separately. (See "Hereditary kidney cancer syndromes", section on 'Management'.)

Translocation renal cell carcinoma (MiT/TFE-related RCC) — A distinct variant of RCC, referred to as translocation renal cell carcinoma, is characterized by a fusion of the *TFE3* (approximately 90 percent), *TFEB*, or *MITF* genes to a number of other genes, including *ASPSCR1*, *PRCC*, *SFPQ*, and *NONO* [158-163].

Translocation renal cell carcinoma tends to occur at a younger age and predominantly in females, as opposed to other RCC histologies that are primarily diagnosed in older male patients [160,163]. Translocation renal cell carcinoma has also been reported in children who have received antecedent chemotherapy for malignancies, autoimmune disorders, or bone marrow transplant conditioning [51]. Translocation renal cell carcinoma presents at a later stage and is associated with a worse prognosis compared with most other RCC histologies [163].

The landscape of molecular alterations in translocation renal cell carcinoma is relatively silent, with fewer pathogenic variants and copy number alterations compared with other RCC histologies, and up to 50 percent of translocation renal cell carcinomas harboring no putative driver alterations beyond the *MiT/TFE* fusion [163-165]. However, some genomic alterations appear to be enriched in translocation renal cell carcinoma compared with other RCC histologies, including 9p loss and 17q gain that have been associated with adverse outcomes in patients with translocation renal cell carcinoma [165,166]. In addition, 9p21.3 (the locus of *CDKN2A* and *CDKN2B*) deep deletions, *TERT* promoter pathogenic variants, and exonic pathogenic variants in genes implicated in DNA damage response and chromatin remodeling all appear to be enriched in translocation renal cell carcinoma [163-165].

The transcriptional program of translocation renal cell carcinoma is distinct from that of other RCC histologies. Transcription is driven by the *MiT/TFE* fusion, and includes upregulation of

pathways implicated in response to reactive oxygen species and xenobiotics, NRF2 signaling, PI3K/mTOR signaling, lysosomal biogenesis, and antiapoptotic genes [123,163,164].

Of note, *TFEB*-amplified renal cell carcinomas have also been reported, whereby the tumors are driven by *TFEB* gene amplification instead of a fusion. These tumors are characterized by amplification of the 6p21.1 locus, where *TFEB* and *VEGFA* are located. These tumors tend to occur in older patients and follow a clinically aggressive course [167,168].

The treatment approach to patients with translocation RCC is further discussed separately. (See "The treatment of advanced non-clear cell renal carcinoma", section on 'Translocation renal cell carcinoma'.)

SMARCB1-deficient renal cell carcinoma and renal medullary carcinoma — Renal medullary carcinoma are tumors that arise from the thick ascending limb of the Loop of Henle in the medulla [169] and are characterized by biallelic loss of *SMARCB1* [170]. Patients with these tumors most frequently have sickle cell trait or disease. The most common mechanisms of *SMARCB1* loss is through deletion and inactivating translocation. Transcriptionally, these tumors most closely resemble collecting duct tumors [170].

The treatment of renal medullary carcinoma is discussed separately. (See "The treatment of advanced non-clear cell renal carcinoma", section on 'Collecting duct and renal medullary carcinoma'.)

Succinate dehydrogenase–deficient renal cell carcinoma — Succinate dehydrogenase-deficient RCCs are characterized by biallelic loss of succinate dehydrogenase (SDH), a key enzyme in the TCA cycle. These renal tumors most commonly arise in the setting of germline pathogenic variants of *SDHB* and are part of a hereditary syndrome that also includes pheochromocytoma/paraganglioma, pituitary adenoma, and gastrointestinal stromal tumors [102]. (See "Paragangliomas: Epidemiology, clinical presentation, diagnosis, and histology", section on 'Familial paraganglioma and SDH pathogenic variants' and "Clinical presentation, diagnosis, and prognosis of gastrointestinal stromal tumors", section on 'GIST syndromes in pediatric and AYA patients' and "Hereditary kidney cancer syndromes", section on 'Succinate dehydrogenase deficiency'.)

However, somatic forms of SDH-deficient RCC have also been described with biallelic (somatic) loss of *SDHB* [170]. These tumors have ubiquitous loss of 1p, which encodes *SDHB.* These tumors have otherwise low tumor mutational burden but harbor frequent copy number alterations [171].

ELOC (TCEB1)-mutated renal cell carcinoma — *ELOC (*formerly *TCEB1)*-mutated RCCs are characterized by biallelic loss of *ELOC* (otherwise known as *TCEB1)* through alterations of the gene with either monosomy 8 or loss of heterozygosity at 8q21. *ELOC* encodes elongin C which is part of the VHL complex. Loss of elongin C leads to HIF accumulation through decreased ubiquitination. These tumors are relatively indolent and typically do not metastasize [172,173].

ALK-rearranged renal cell carcinomas — ALK-rearranged RCCs are very rare tumors that are characterized by an *ALK* translocation. These tumors respond dramatically to treatment with ALK inhibitors [174,175].

Other tumor types — Several other entities in the 2022 World Health Organization (WHO) classification of kidney tumors include mucinous tubular and spindle cell carcinoma, tubulocystic carcinoma, clear cell papillary RCC, acquired cystic disease-associated RCC, eosinophilic solid and cystic RCC, and others [101,102,176]. Rare primary malignancies that have been reported to arise in the kidney include lymphomas [177], soft tissue sarcomas (eg, leiomyosarcoma, liposarcoma) [178], and carcinoids [179].

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Cadmium toxicity (The Basics)")
- Beyond the Basics topic (see "Patient education: Renal cell carcinoma (kidney cancer) (Beyond the Basics)")

SUMMARY

- **General principles** – Renal cell carcinomas (RCCs) are the most common primary tumor arising in the kidney, accounting for approximately 80 to 85 percent of such tumors. (See 'Introduction' above.)

  Transitional cell carcinomas arising in the renal pelvis account for approximately 8 percent, while other rare tumors comprise the rest. (See "Malignancies of the renal pelvis and ureter".)

- **Incidence** – The incidence of RCC has been steadily increasing in the United States, while the size of primary RCCs has been gradually decreasing. These trends have been attributed, in part, to the diagnosis of asymptomatic tumors using noninvasive abdominal imaging modalities. (See 'Epidemiology' above.)

- **Risk factors** – Risk factors associated with a significantly increased incidence of RCC include smoking, obesity, hypertension, and others. RCC has also been associated with a variety of inherited syndromes. (See 'Established risk factors' above and "Hereditary kidney cancer syndromes".)

- **Pathology** – RCC is classified into the following pathologic tumor subtypes, at the following frequencies (see 'Pathology' above):

  - Clear cell (75 to 85 percent of tumors) – (see 'Clear cell carcinomas' above)
  - Papillary (10 to 15 percent) – (see 'Papillary carcinomas' above)
  - Chromophobe (5 to 10 percent) – (see 'Chromophobe carcinomas' above)
  - Oncocytic (3 to 7 percent) – (see 'Oncocytomas' above)
  - Collecting duct (very rare) – (see 'Collecting duct tumors' above)
  - Molecularly-defined renal cell carcinomas (rare) – (See 'Molecularly defined renal cell carcinomas' above.)

- **Molecular alterations in the *VHL* gene and RCC** – Abnormalities of the von Hippel-Lindau (*VHL*) tumor suppressor gene are implicated in most cases of clear cell RCC (both sporadic and familial). (See 'Von Hippel-Lindau gene' above and "Molecular biology and pathogenesis of von Hippel-Lindau disease" and "Clinical features, diagnosis, and management of von Hippel-Lindau disease", section on 'VHL somatic pathogenic variants in sporadic tumors'.)

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