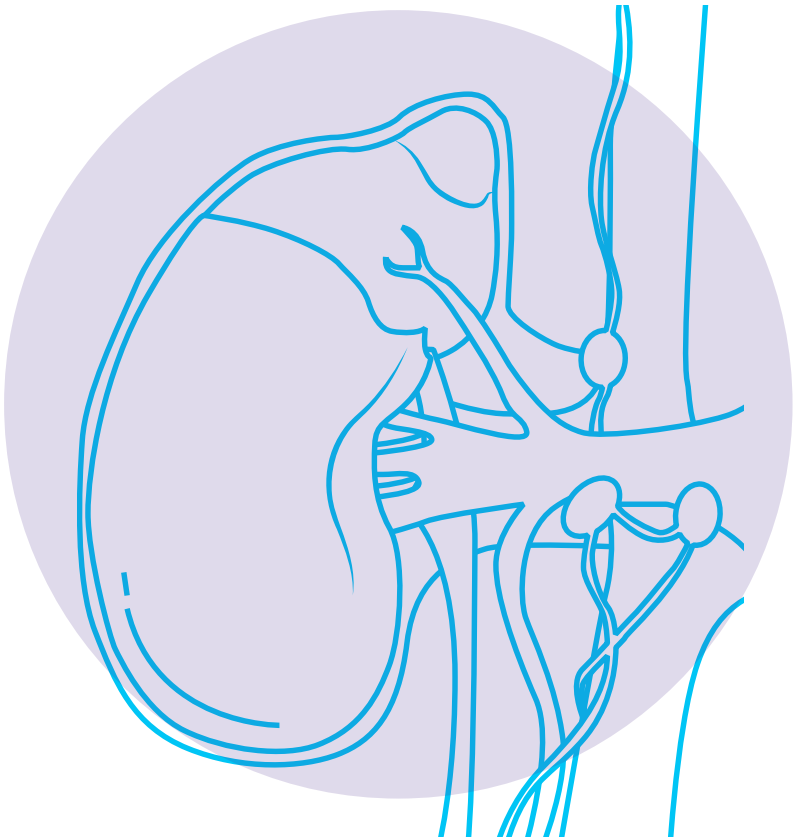
Renal Cell Carcinoma

Disease State

US-AVE-01274
September 2023

Content

RCC subtypes



RCC arises from the renal epithelium, representing **>90%** of renal malignancies.[1] RCC is composed of several different subtypes, which differ in several ways[1]

- Major subtypes (4% incidence) include clear cell RCC (ccRCC), papillary RCC (pRCC), chromophobe RCC (chRCC)[1]
- Unclassified RCC (uRCC)[1]
- Other subtypes are very rare, each with **≤1%** total incidence[1]
- RCC with sarcomatoid differentiation (sRCC), characterized by a spindle-like morphology, high cellularity, and atypia, is a highly aggressive form of RCC.[2] These features are found in 5–8% ccRCC, 8–9% of chRCC, and 2–3% of pRCC[2]

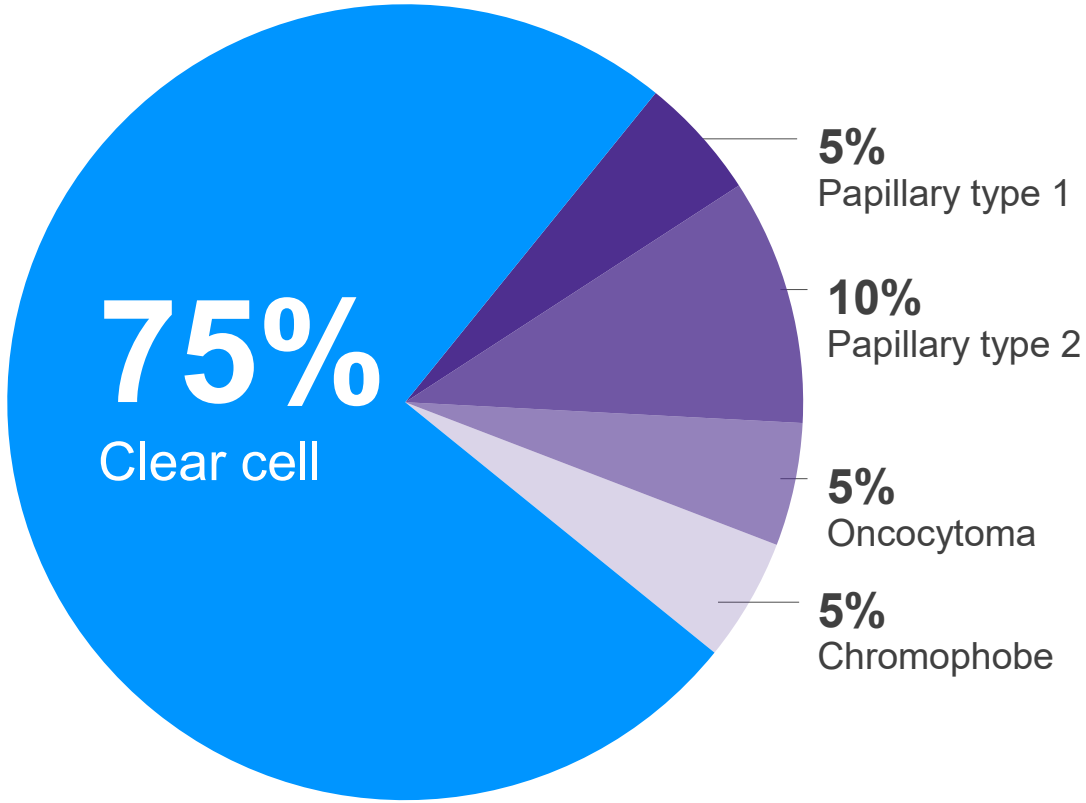
There is significant intra- and intertumor heterogeneity in ccRCC, which could contribute to observed heterogeneous clinical outcomes[1]

ccRCC, clear cell renal cell carcinoma; chRCC, chromophobe renal cell carcinoma; pRCC, papillary renal cell carcinoma; RCC, renal cell carcinoma; uRCC, unclassified renal cell carcinoma.

1. Hsieh JJ, et al. Nat Rev Dis Primers. 2018;3:17009; 2. Pichler R, et al. Cancers (Basel). 2019;11(3):422.

Most common RCC subtypes

INCIDENCE (%)[1,2]



- RCC is a heterogeneous group of diseases[1]
- Of all kidney tumors, >90% are RCC[1]
- Different neoplasms of the kidney are characterized by distinct histologies, genetic alterations, clinical course, and response to therapy[1,2]

RCC, renal cell carcinoma.

1. Hsieh JJ, et al. Nat Rev Dis Primers. 2018;3:17009; 2. Linehan WM, et al. J Urol 2003;170:2163–72.

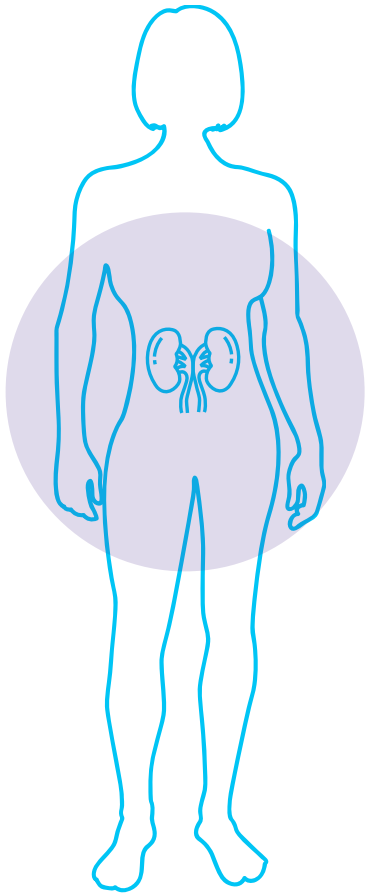
Morphological and clinical differences in RCC subtypes

RCC subtype	Clinical features[1–4]	Morphological/ immunohistochemical features[1]	Molecular features[1,4]
ccRCC	65–70% of adult RCCs (5% associated with hereditary syndromes)	Clear/eosinophilic cells with thin-walled, staghorn-shaped vasculature; positive for CAIX and CD10, negative for CK7 and AMACR	LOF of VHL syndrome; Chr 3p deletion; HIF stabilization; PI3K/AKT pathway mutations; *SETD2*, *BAP1,* and *MTOR* mutations, aggressive ccRCC demonstrating a metabolic shift
pRCC	15–20% of adult RCCs; Type 1 shows a better prognosis than Type 2 as it is detected earlier at lower grades; CIMP-RCC is associated with early-onset disease and poor survival	Papillary structure, foamy macrophages; Type 1: scanty cytoplasm Type 2: abundant eosinophilic cytoplasm; positive for CD10, CK7 and AMACR, negative for CAIX	Gain of Chr 7 and/or Chr 17, loss of Chr Y; three subtypes according to the TCGA: Type 1: MET alteration Type 2: CDKN2A silencing; SETD2 mutation CIMP-RCC: CpG island methylation; fumarate hydratase mutation
chRCC	5–7% of adult RCCs; favorable prognosis; most frequent subtype in patients in 6th decade of life; associated with Birt–Hogg–Dubé syndrome with an *FLCN* mutation	Prominent cell membrane, irregular nuclei, perinuclear halo, pale to eosinophilic cytoplasm; positive for KIT and CK7, negative for CAIX and CD10	Loss of Chrs 1, 2, 6, 10, 13, and 17; somatic mutation in mitochondrial DNA; mutations of *TP53* and *PTEN;* imbalanced chromosome duplication; high TERT expression by DNA rearrangement within the TERT promoter region with kataegis

AMACR, alpha-methylacyl-CoA racemase; BAP1, BRCA1-associated protein 1; CAIX, carbonic anhydrase 9; ccRCC, clear cell renal carcinoma; chRCC, chromophobe renal cell carcinoma; CD10, neprilysin; CIMP-RCC, CpG island methylator phenotype renal cell carcinoma; CK7, cytokeratin-7; FLCN, folliculin; HIF, hypoxia-inducible factor; MET, mesenchymal-epithelial transition; mTOR, mechanistic target of rapamycin kinase; pRCC, papillary renal cell carcinoma; PTEN, phosphatase and tensin homolog; SETD2, SET domain containing 2; TP53, tumor protein p53; VHL, Von Hippel-Lindau.

1. Inamura K, et al. Int J Mol Sci. 2017;18:2195; 2. Linehan WM, et al. J Urol. 2003;170:2163–72; 3. Muglia VF, et al. Radiol Bras. 2015;48:166–74; 4. Ricketts CJ, et al. Cell Rep. 2018;23(1):313–26.

Metastasis



Approximately

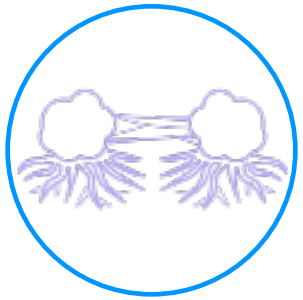
30%

of patients who are thought to have non-metastatic disease, based on initial clinical and pathological evaluation, have occult metastases that will eventually become clinically evident[1]

Patients with ccRCC are believed to have the highest risk of metastasis, and the poorest survival after the pRCC subtype CIMP-RCC[2,3]

83–88%

of metastatic disease demonstrates a clear cell histology, and all other metastatic tumors are denoted non-clear cell RCC (nccRCC)[1]



Despite morphological similarities, there are molecular differences between the primary and metastatic tumors. The relevance of these differences to disease management has yet to be understood[4]

ccRCC, clear cell renal cell carcinoma; CIMP-RCC, CpG island methylator phenotype renal cell carcinoma; nccRCC, non-clear cell renal cell carcinoma; pRCC, papillary renal cell carcinoma; RCC, renal cell carcinoma.

1. Hsieh JJ, et al. Nat Rev Dis Primers. 2018;3:17009; 2. Patard JJ, et al. J Clin Oncol. 2005;23(12):2763–71; 3. Ricketts CJ, et al. Cell Reports. 2018;23:313–26; 4. Semeniuk-Wojtaś A, Stec R, Szczylik C. Urol Oncol. 2016;34(5):215–20.

Key mutations in ccRCC

Gene	Commonality in tumor samples[1]	Function[1]	Location[1]	Association with disease state and treatment[1]
PBRM1	29–41%	Chromatin and histone regulating proteins; tumor suppressor	3p21	Associated with stage III pathological features
SETD2	8–12%		3p21	Associated with reduced relapse-free survival
BAP1	6–10%		3p21	Associated with larger tumor size, higher Fuhrman nuclear grade, and worse survival
KDM5C	4–7%	Lysine demethylase	Xp.11	Correlated with therapeutic benefit from targeted therapy
MTOR	5–6%	Regulation of protein translation and cell growth; mutations are activating		*MTOR* mutations in ccRCC increase function and may promote sensitivity to mTOR inhibitors

In addition to *VHL*, there are other commonly mutated genes in ccRCC. Loss of Chromosome 3p (common in ccRCC) leads to haploinsufficiency of multiple tumor suppressors (*VHL*, *PBRM1, SETD2, BAP1).*[1] Mutations in *PBRM1, SETD2,* and *BAP1* are usually mutually exclusive, and one study showed *SETD2* mutations to vary across metastatic loci, suggesting a role for *SETD2* loss in tumor progression to metastatic capability[1,2]

BAP1, BRCA1-associated protein 1; ccRCC, clear cell renal cell carcinoma; *KDM5C*, lysine demethylase 5C; *MTOR*, mechanistic target of Rapamycin kinase; *PBRM1*, polybromo 1; *SETD2*, SET domain containing 2; VHL, Von Hippel-Lindau.

1. Hsieh JJ, et al. Nat Rev Dis Primers. 2018;3:17009; 2. Greef B, Eisen T. BJC. 2016;115:505–26.

Common chromosomal alterations in RCC

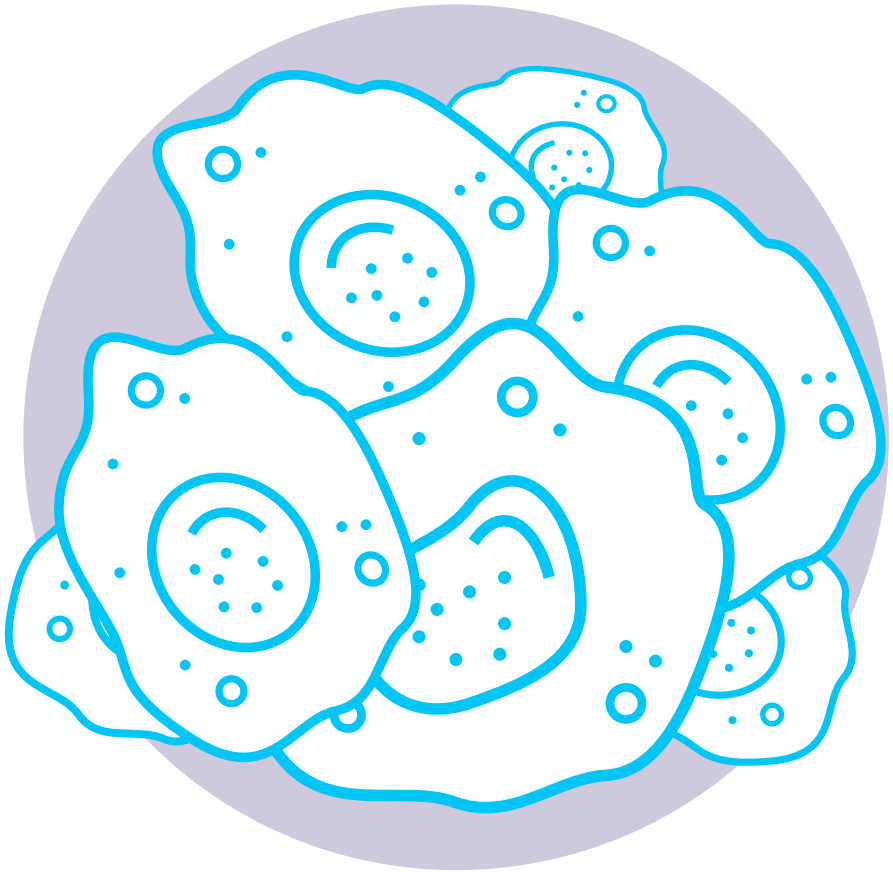
ccRCC	LOH in 3p (most common), chromosomes 14, 8, 9 and 6 (20–40%) and chromosomes 1, 4, 10q, 13q, 17p, and 18q (less frequent)
pRCC	Trisomy of chromosomes 7 and 17 and loss of the Y chromosome; LOH in 9p and in chromosomes 6, 8, and 14
chRCC	Monosomy of chromosomes 1, 2, 6, 10, 13, 17, and 21 in 75–100% of tumors; deletion of 3p, 8p, and 9p in up to 25% of tumors
Collecting duct and other rare forms of RCC	LOH of chromosome 1q, 6p, 8p, 13q and 21q

- Differences in common chromosomal rearrangements are observed across RCC subtypes[1]
- RCC subtypes have also shown different transcriptional programs[2]

ccRCC, clear cell renal cell carcinoma; chRCC, chromophobe renal cell carcinoma; LOH, loss of heterozygosity; pRCC, papillary renal cell carcinoma; RCC, renal cell carcinoma.

1. Cairns P. Cancer Biomark. 2011;9(1–6):461–73; 2. Lindgren D, et al. Cell Reports. 2017;20:1476–89.

Tumor heterogeneity overview[1]



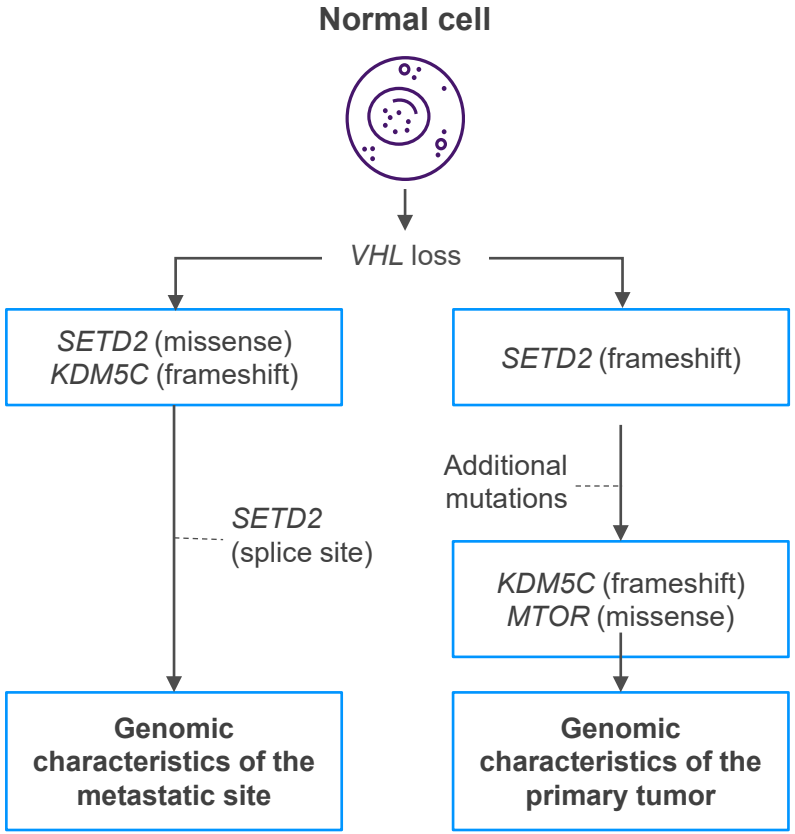
- Tumor temporal and spatial heterogeneity is believed to be due to genetic instability, allowing for genomic alterations as the tumor grows and develops
- Mutations occurring subsequent to the most recent common ancestor (MRCA) promote subclone formation and evolution

MRCA, most recent common ancestor.

1. Hsieh JJ, et al. Nat Rev Dis Primers. 2018;3:17009.

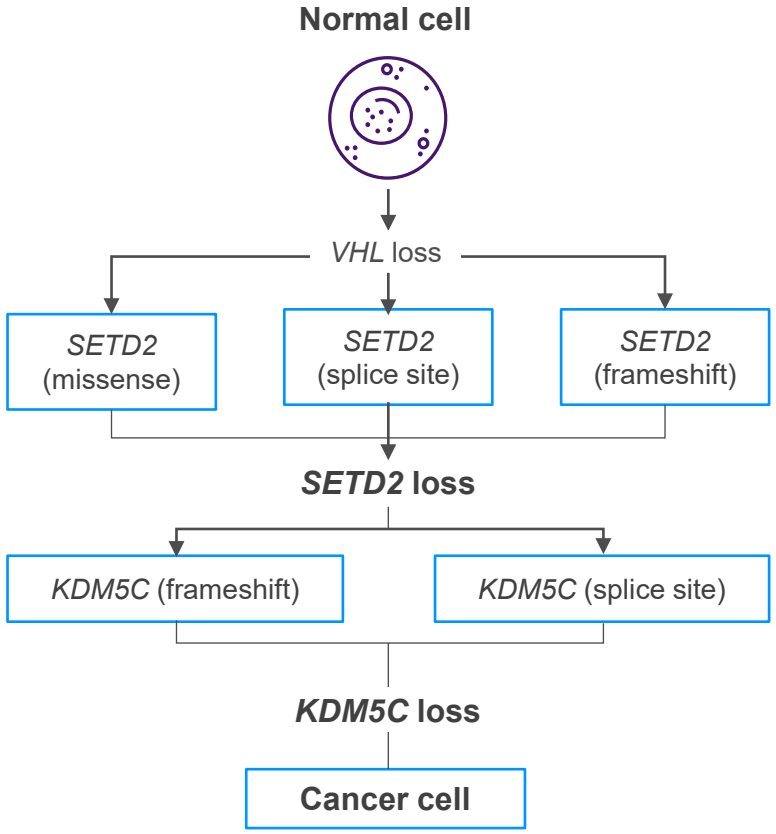
Tumor heterogeneity at the mutation level

PHYLOGENETIC TREE MODEL



Phylogenetic tree showing tumor divergence with different mutations across subclones

BRAIDED RIVER MODEL



Braided river model showing different mutations in key driver proteins with similar outcomes can allow for tumor convergence

- Mutations commonly observed across the tumor (ie, *VHL* mutations and 3p LOH in ccRCC) are considered to be early events in disease pathogenesis, occurring in a common ancestor cell
- Although mutations in key disease drivers occurring beyond the MRCA may be distinct genetic events (ie, *SETD2*), they may have the same effect on protein function and, thus, consequence for the tumor cell. This parallel evolution has been suggested to represent tumor convergence

ccRCC, clear cell renal cell carcinoma; *KDM5C*, lysine demethylase 5C; LOH, loss of heterozygosity; MTOR, mechanistic target of Rapamycin kinase; MRCA, most recent common ancestor; *SETD2*, SET domain containing 2; VHL, Von Hippel-Lindau.

1. Hsieh JJ, et al. Nat Rev Dis Primers. 2018;3:17009.

Biomarkers

- Unlike other cancers, RCC does not carry a high mutational load; analysis by MSKCC Score suggested no trend with stratification by risk group[1]
- No differences in expression of T cell effector molecules (granzyme A and perforin) or checkpoint expression were observed by MSKCC risk group[2]

PROGNOSTIC AND PREDICTIVE BIOMARKERS IN RCC[1]

Biomarker	Association	Biomarker	Association
Gene alterations in *BAP1*	Worse overall survival	**Negative IHC expression for BAP1**	Better mTOR inhibitor response
Gene alterations in *PBRM1*	Better overall survival		
PBRM1 wild type + gene alterations *BAP1*	Worse overall survival	**Negative IHC expression for PBRM1**	Better mTOR inhibitor response
Gene alterations in *KDM5C*	Better overall survival		
PDCD1, CTLA4 and TLR9	Worse overall survival	**SETD2, TP53, and VHL**	Not associated with prognosis
9p deletion	High risk of recurrence and RCC-specific mortality		

BAP1, BRCA1-associated protein 1; *KDM5C*, lysine demethylase 5C; MSKCC, Motzer score for renal cell carcinoma; mTOR, mammalian target of rapamycin; PBRM1, protein polybromo-1; RCC, renal cell carcinoma; SETD2, SET Domain Containing 2; TP53, tumor protein p53; VHL, Von Hippel-Lindau.

1. Lopez-Beltran A, et al. Front Oncol. 2018;8. doi:10.3389/fonc.2018.00456; 2. de Velasco G, et al. Cancer Immunol Res. 2016;4(10):820–2.

Metabolic changes

- Metabolic reprogramming is common in cancer, allowing for sufficient energy and cellular resources to support the higher rate of cell proliferation.[1] The Warburg effect describes the phenomenon where cancer cells increase glucose uptake for aerobic glycolysis, suggested to be necessary for processes supporting tumor growth and survival, including immune evasion[2]
- One study reported the Warburg effect to occur in RCC, in line with a reduction in subsequent stages of cellular respiration, the TCA cycle, and oxidative metabolism[3]
- Differential expression of Krebs cycle genes were observed across subtypes, with highest expression in Type 2 pRCC. Glycolytic gene expression was higher in ccRCC and Type 2 pRCC. Ribose sugar metabolism was also altered in pRCC[4]
- Both primary and secondary ccRCC samples, as well as pRCC and chRCC samples, demonstrated an increase in glycolysis-associated metabolites and a decrease in TCA cycle metabolites as compared to non-tumor tissue, suggesting a change in these processes. Increased glutamine has also been reported in ccRCC[5]
- Changes in the tryptophan pathway have also been observed, including increased levels of the immunosuppressive metabolite kynurenine[5]
- Some studies report additional metabolic changes with tumor grade, suggesting a metabolic shift with progression[5,6]

ccRCC, clear cell renal cell carcinoma; chRCC, chromophobe renal cell carcinoma; pRCC, papillary renal cell carcinoma; RCC, renal cell carcinoma.

1. Hanahan D, Weinberg RA. Cell. 2011;144(5):646–74; 2. Liberti MV, Locasale JW. Trends Biochem Sci. 2016;41(3):211–8; 3. Wettersten H, et al. Cancer Res. 2015;75(12):2541–52;
4. Ricketts CJ, et al. Cell Reports. 2018;23:313–26; 5. Schaeffeler E, et al. Eur Urol Focus. 2018. pii: S2405–4569(18)30017–8; 6. Hakimi AA, et al. Cancer Cell. 2016;29(1):104–16.

Immune engagement

- Numerous studies have explored the interaction between the immune system and RCC[1–9]
- A shift is observed from a Type-1 (via Th1 helper T cells) antitumor response to a Type-2 (via Th2 helper T cells) response allowing tumor immune evasion.[1–3] Type-2 signaling has been associated with T_{regs}, and Type-2 gene expression signature has been associated with poor survival[1,2,4]
- RCC tumors are characterized by high immune cell infiltration.[5] T-cell number was shown to increase with tumor grade and inversely correlate to patient survival.[6] Ratio of CD8+ T cells to T_{reg} cells (but not CD8+ abundance alone) was associated with survival.[5] Further, markers of T-cell exhaustion also correlated with disease grade and stage[7]
- Anti-tumor immune effectors, NK cells, were also found to decrease with disease progression, whereas tumor-supporting and immunosuppressive cells, such as MDSCs and tumor-associated macrophages, increased[6,8,9]

MDSC, myeloid-derived suppressor cells; RCC, renal cell carcinoma.

1. Aparicio LMA, Fernandez IP, Cassinello J. Clin Transl Oncol. 2017;19(10):1175–82; 2. Finke JH, et al. Clin Cancer Res. 2008;14(20):6674–82; 3. Pulendran B, Artis D. Science. 2012;337(6093):431–5; 4. Ricketts CJ, et al. Cell Reports. 2018;23:313–26; 5. Şenbabaoğlu Y, et al. Genome Biology. 2016;17:231; 6. Geissler K, et al. OncoImmunology. 2015;4:1,e985082; 7. Chevrier S, et al. Cell. 2017;196(4):736–49; 8. Guan X, et al. Adv Clin Exp Med. 2018;27(7):947–953; 9. Komohara Y, et al. Cancer Sci. 2011;102(7):1424–31.

VEGF signaling

- VEGF signaling, downstream of VHL loss and HIF stabilization, increases angiogenesis, supporting tumor growth and progression.[1–3] However, vascularization is believed to be by abnormal blood vessels, decreasing immune cell infiltration and drug delivery, while increasing hypoxia and cancer cell shedding[1,3,4]
- VEGF signaling is also believed to promote an immunosuppressive tumor microenvironment by[1,5–7]:
  - Inhibiting cytotoxic T-cell trafficking, proliferation, and function
  - Inhibiting dendritic cell maturation and antigen presentation, thus diminishing the T cell-mediated anti-tumor immune response
  - Promoting the recruitment and proliferation of immunosuppressive cells, including T_{reg} cells, MDSCs, and tumor-associated macrophages
  - Altering expression of ligands on endothelial cells and promoting endothelial cell energy, affecting immune cell trafficking to the tumor site

HIF, hypoxia-inducible factor; MDSC, myeloid-derived suppressor cells; VEGF, vascular endothelial growth factor; VHL, Von Hippel-Lindau.

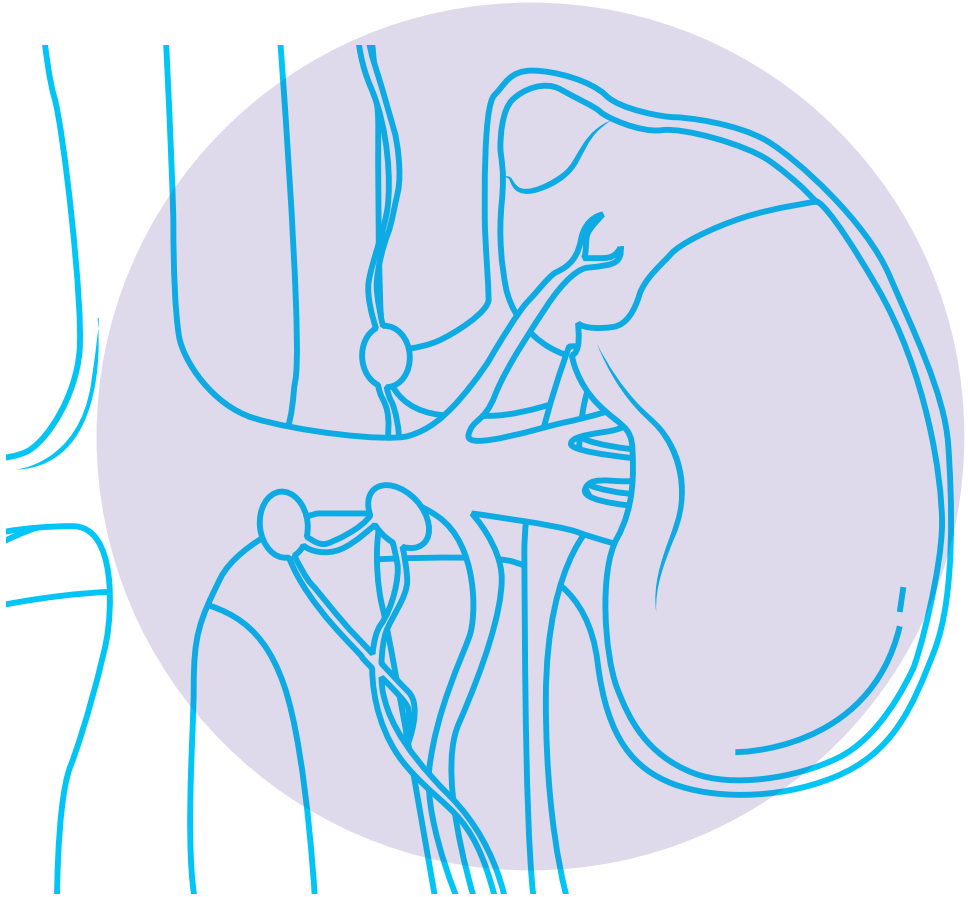
1. Fukumura D, et al. Nat Rev Clin Oncol. 2018;15(5):325–40; 2. Cowey CL, Rathmell WK. Curr Oncol Rep. 2009;11(2):94–101; 3. Broadaczewska KK, Szczylik C, Kieda C. Contemp Oncol (Pozn). 2018; 22(1A):14–2; 4. Perier A, et al. Oncogene. 2011;30:2622–32; 5. Bouzin C, et al. J Immunol. 2007;178:1505–11; 6. Gabrilovich D, et al. Blood.1998;92:4150–66; 7. Pircher A, et al. Int J Mol Sci. 2017;18(2291):1–15.

Signs and symptoms

Kidney cancer rarely causes visible signs or symptoms in its early stages. However, symptoms might become apparent in the later stages of the disease.[1]

POSSIBLE SIGNS AND SYMPTOMS OF KIDNEY CANCER MAY INCLUDE[1]:

- Blood in the urine (hematuria)
- Lower back pain on one side
- A mass (lump) on the side or lower back
- Fatigue
- Loss of appetite
- Weight loss
- Persistent fever that is not caused by infection
- Anemia



1. ACS. Revised February 2023. Kidney cancer signs and symptoms. https://www.cancer.org/cancer/kidney-cancer/detection-diagnosis-staging/signs-and-symptoms.html (accessed 30 June 2023).

Diagnosis[1]

- >50% of RCC cases are currently detected incidentally; however, suspicion of RCC should prompt the following laboratory examinations:
  - **Serum creatinine**
  - **Hemoglobin**
  - **Leukocyte and platelet counts**
  - **Lymphocyte-to-neutrophil ratio**
  - **Lactate dehydrogenase**
  - **C-reactive protein**
  - **Serum-corrected calcium**
- Ultrasonography and CT scans are typically used to diagnose RCC, and allow assessment of local invasiveness, lymph node involvement, and distant metastases
- MRI might provide additional information on local advancement and venous involvement by tumor thrombus
- Biopsy provides histopathological confirmation of malignancy
- Contrast-enhanced chest, abdominal, and pelvic CT is mandatory for accurate staging

RCC, renal cell carcinoma.

1. Escudier B, et al. Ann Oncol 2016;27(Suppl 5):v58–v68.

Disease classification – grade and stage

Staging of RCC is based on size, position, and lymph node involvement, and treatment is largely guided by stage[1]

STAGE I

- Tumor <7 cm in the largest dimension
- Limited to the kidney
- 5-year survival rate of 95%

Management options

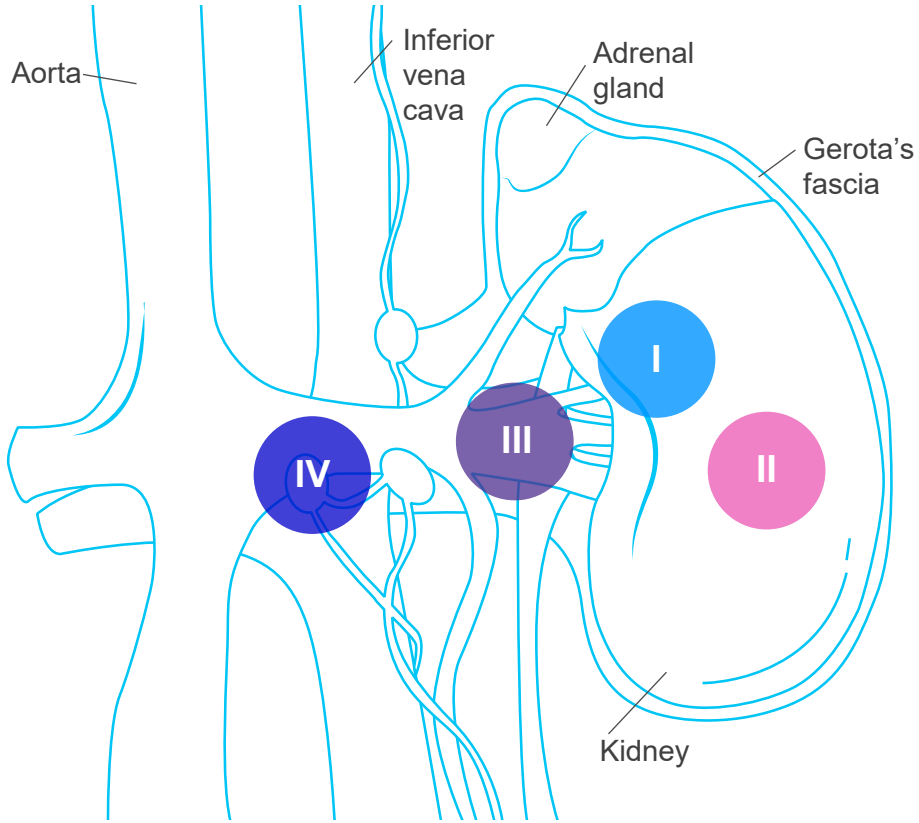
- Partial nephrectomy
- If not technically feasible, active surveillance or ablative therapies in selected patients with small masses

STAGE III

- Tumor in the major veins or adrenal gland with an intact Gerota's fascia
- Or one regional lymph node involved
- 5-year survival rate of 59%

Management options

- Radical nephrectomy plus adrenalectomy, tumor thrombus excision (if appropriate), and/or lymph node dissection
- Systemic treatment if inoperable or owing to poor performance status



STAGE II

- Tumor <7 cm in the largest dimension
- Limited to the kidney
- 5-year survival rate of 88%

Management options

- Radical nephrectomy
- Partial nephrectomy in selected patients in whom the procedure is feasible

STAGE IV

- Tumor beyond Gerota's fascia
- Or more than one regional lymph node involved
- Data metastases
- 5-year survival rate of 20%

Management options

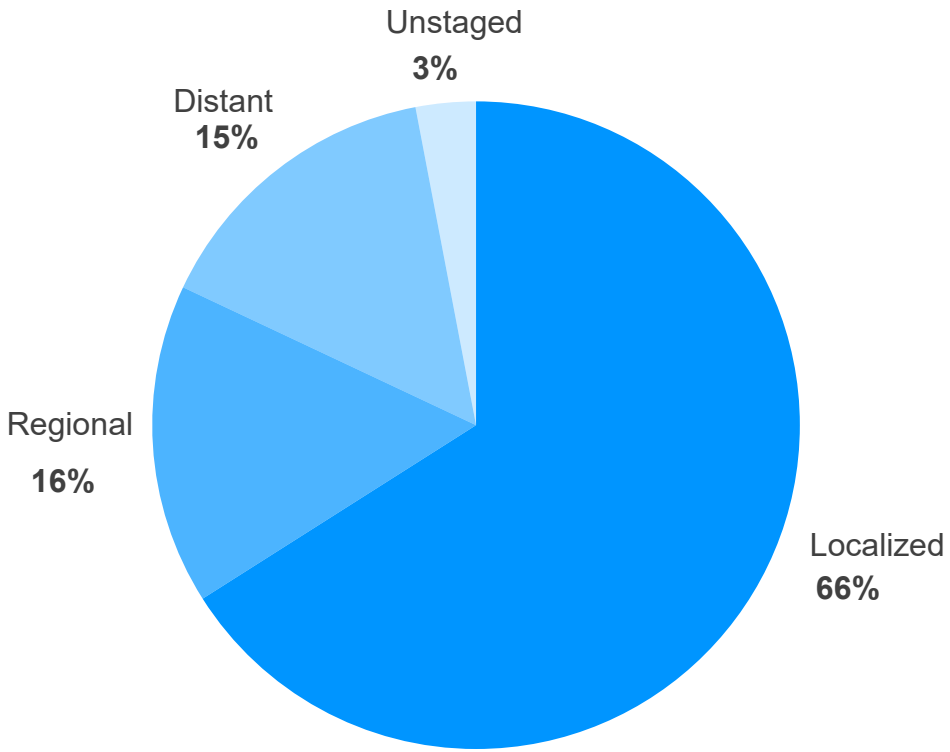
- Radical nephrectomy plus adrenalectomy, tumor thrombus excision (if appropriate), and/or lymph node dissection
- Systemic treatment if inoperable, distant metastases, or owing to poor performance status

RCC, renal cell carcinoma.

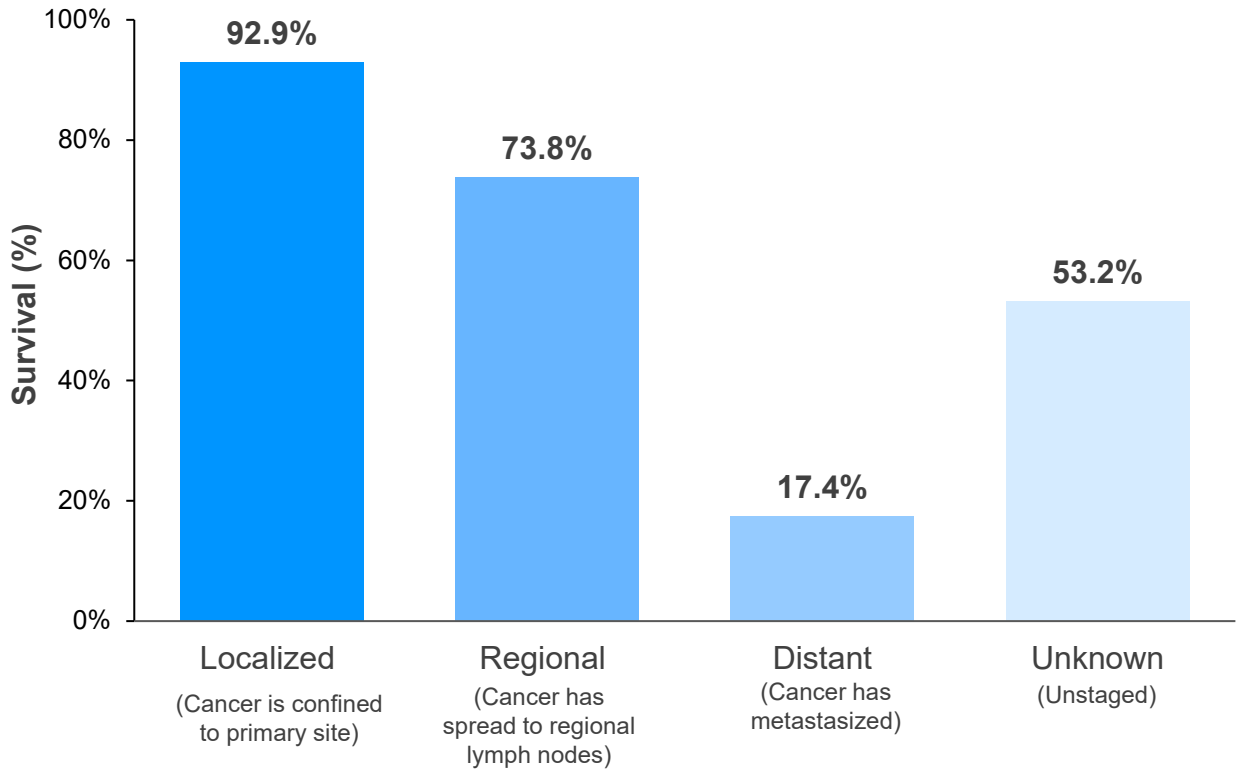
1. Hsieh JJ, et al. Nat Rev Dis Primers. 2018;3:17009.

Stage at diagnosis of kidney and renal pelvis cancer is linked with survival[1]

PROPORTION OF PATIENTS WITH DIFFERENT DISEASE STAGES AT DIAGNOSIS[1,*]



5-YEAR RELATIVE SURVIVAL VARIES ACCORDING TO DISEASE STAGE AT DIAGNOSIS[1,*]



*SEER 22 (Excluding IL/MA) 2013–2019, All races, Both Sexes by SEER Combined Summary Stage.

1. National Cancer Institute. SEER stat fact sheets: kidney and renal pelvis cancer. http://seer.cancer.gov/statfacts/html/kidrp.html (accessed 30 June 2023).

Risk factors for RCC incidence

Non-modifiable[1–3]

Age

Sex (2:1 male to female ratio)

Ethnicity

Height

Family history (especially when sibling is affected)

Thyroid carcinoma

Prior radiotherapy

Advanced kidney disease

- Chronic kidney disease
- Hemodialysis
- Kidney transplant

Acquired cystic kidney disease

- End-stage renal disease on maintenance dialysis

Genetics

- Von Hippel-Lindau syndrome
- Hereditary papillary RCC
- Hereditary leiomyomatosis RCC
- Birt–Hogg–Dubé syndrome

Modifiable[1,2]

Obesity

Smoking

Hypertension

Drugs

- Acetaminophen
- Nonsteroidal anti-inflammatory drugs
- Aristolochic acid
- Occupational exposure to arsenic/cadmium/trichloroethylene

Multiparous females

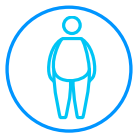
Risk factors for RCC range from genetic to environmental, some of which can be reduced or removed[1,2]

RCC, renal cell carcinoma.

1. ACS. Revised February 2023. Risk factors for kidney cancer. https://www.cancer.org/cancer/kidney-cancer/causes-risks-prevention/risk-factors.html (accessed 30 June 2023); 2. Graves A, et al. Immunotargets Ther. 2013;2:73–90; 3. Hsieh JJ, et al. Nat Rev Dis Primers. 2018;3:17009.

Key risk factors[1,2]

SMOKING
Smokers are at greater risk than non-smokers



OBESITY
Strong link between excess weight (in men and women) and RCC

AGE[2]
The median age of people at diagnosis is 65 years

GENDER
RCC is twice as common in men as in women

RACE[2]
Non-Hispanic Americans/Indian Alaska Natives have higher rates of RCC than other races

GENETICS
Genetic risk factors and several rare inherited conditions can cause RCC (see next slide)

FAMILY HISTORY
- People with a family history of RCC have an increased risk
- Risk is highest in individuals with a sibling with RCC

HIGH BLOOD PRESSURE
Those with high blood pressure have a higher risk of RCC; it is not known whether this is due to the condition or antihypertensive medication (or both)

ADVANCED KIDNEY DISEASE
Those requiring dialysis are especially at risk

WORKPLACE EXPOSURES
Exposure to cadmium, some herbicides, and organic solvents (particularly trichloroethylene) can increase the risk of RCC

RCC, renal cell carcinoma.

1. ACS. Revised February 2023. Risk factors for kidney cancer. https://www.cancer.org/cancer/kidney-cancer/causes-risks-prevention/risk-factors.html (accessed 30 June 2023);
2. National Cancer Institute. SEER stat fact sheets: kidney and renal pelvis cancer. http://seer.cancer.gov/statfacts/html/kidrp.html (accessed 30 June 2023).

Hereditary syndromes associated with RCC1

Syndrome	Gene	Renal cancer type
BAP1 mutant disease	*BAP1*	Clear cell
Birt–Hogg–Dubé syndrome	*FLCN*	Oncocytic, chromophobe
Familial clear cell renal cancer with Chromosome 3 translocation	Transloc chr 3	Clear cell
Hereditary leiomyomatosis and RCC	*FH*	Papillary type 2
Hereditary papillary renal cancer	*MET*	Papillary type 1
PTEN hamartoma syndrome	*PTEN*	Clear cell
SDH-associated renal cancer	*SDHB* *SDHC* *SDHD*	Clear cell, chromophobe, oncocytoma
Tuberous sclerosis complex	*TSC1* *TSC2*	Angiomyolipoma Epitheliod angiomyolipoma
Von Hippel-Lindau syndrome	*VHL*	Clear cell

Hereditary kidney cancer accounts for

3–5%

of all kidney cancer

10

inherited cancer susceptibility syndromes are associated with inherited risk of kidney cancer, **with 12 genes identified**

BAP1, BRCA1-associated protein 1; FH, familial hypercholesterolemia; FLCN, folliculin; MET, mesenchymal-epithelial transition; PTEN, phosphatase and tensin homolog; RCC, renal cell carcinoma; SDH, succinate dehydrogenase; SDHB, succinate dehydrogenase complex B; SDHC, succinate dehydrogenase complex C; SDHD, succinate dehydrogenase complex D.

1. Haas NB, Nathanson KL. Adv Chronic Kidney Dis. 2014;21(1):81–90.

Genetic and hereditary risk factors

THE FOUR MAJOR, AUTOSOMAL-DOMINANT, HERITABLE RCC SYNDROMES RECOGNIZED BY THE NATIONAL CANCER INSTITUTE[1-3]

Syndrome	Gene locus, gene type (protein)	Renal tumor pathology type	Non-renal tumors and associated abnormalities	Cumulative lifetime cancer risk
Von Hippel-Lindau (VHL) syndrome[1]	VHL 3p26, tumor suppressor (pVHL)	Clear-cell RCC (multifocal)	CNS hemangioblastoma, retinal hemangioblastomas, pheochromocytoma, pancreatic neuroendocrine tumor, endolymphatic sac tumor, cystadenoma of the pancreas, the epididymis, and the broad ligament	24–45%
Hereditary papillary renal carcinoma[2]	MET 7q31.2, proto-oncogene (hepatocyte growth factor receptor)	Papillary type 1	None known	Approaching 100%
Birt–Hogg–Dubé syndrome[1]	FLCN 17p11.2, tumor suppressor (folliculin)	Chromophobe, hybrid oncocytic, papillary, clear-cell, oncocytoma	Cutaneous: fibrofolliculomas/ trichodiscomas Pulmonary: lung cysts, spontaneous pneumothoraces	15–30%
Hereditary leiomyomatosis and RCC[3]	FH 1q42.3-43, tumor suppressor (fumarate hydratase)	'HLRCC-type RCC' may be new entity (formerly called papillary type 2)	Cutaneous leiomyomas, uterine leiomyomas (fibroids)	Up to 30%

These pathogenic variants are estimated to account for

5–8%

of RCC cases[1]

FH, familial hypercholesterolemia; FLCN, folliculin; HLRCC, hereditary leiomyomatosis renal cell carcinoma; MET, mesenchymal-epithelial transition; RCC, renal cell carcinoma; VHL, Von Hippel-Lindau.

1. Genetics of Renal Cell Carcinoma. National Cancer Institute website. Revised April 2023. https://www.cancer.gov/types/kidney/hp/kidney-genetics-pdq#section/_24 (accessed 10 September 2023); 2. Hereditary Papillary Renal Carcinoma. National Cancer Institute website. Revised December 2022. https://www.cancer.gov/types/kidney/hp/renal-cell-carcinoma-genetics/hprc-syndrome (accessed 10 September 2023); 3. Hereditary Leiomyomatosis and Renal Cell Cancer. National Cancer Institute website. Revised December 2022. https://www.cancer.gov/types/kidney/hp/renal-cell-carcinoma-genetics/hlrcc-syndrome (accessed 10 September 2023)

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Von Hippel-Lindau (VHL)

- VHL regulates the stability of HIF-1a and HIF-2a, transcription factors that increase expression of proangiogenic genes in response to hypoxia (ie, *VEGF*), a common state experienced by tumors which limits their growth[1]
- Loss of function *VHL* mutations allow for HIF stabilization and accordingly increased HIF-mediated transcription, leading to several outcomes, including angiogenesis and tumor survival[1]
- In ccRCC, *VHL* is one of the most commonly dysregulated genes through both genetic and epigenetic mechanisms.[1] *VHL* mutation is believed to be the earliest oncogenic change, potentially occurring prior to tumor formation and, thus, serving as a driving event in ccRCC tumorigenesis.[1–2] However, other alterations are necessary, as studies show that mere loss of VHL is not sufficient to generate tumors[2]
- Accordingly, most ccRCC tumors are highly vascularized.[1] Numerous treatment options act through blocking VEGF-mediated–increased angiogenesis downstream of HIF signaling.[2] The success of this approach confirms the role of increased vascularization in ccRCC[2]
- VEGF signaling has been linked to immune suppression[3,4]

ccRCC, clear cell renal cell carcinoma; HIF, hypoxia-inducible factor; VHL, Von Hippel-Lindau; VEGF, vascular endothelial growth factor.

1. Schönenberger D, et al. Oncotarget. 2016;7(38):60971–85; 2. Hsieh JJ, et al. Nat Rev Dis Primers. 2018;3:17009; 3. Terme M, Tartour E, Taieb J. Cancer Res. 2013;73:539–49; 4. Fukumura D, et al. Nat Rev Clin Oncol. 2018;15(5):325–40.

HPRCC and HLRCC

HEREDITARY PAPILLARY RENAL CELL CARCINOMA (TYPE 1 PAPILLARY) – HPRCC[1]

- HPRCC is an autosomal dominant syndrome characterized by multifocal, bilateral type I papillary RCCs
- Mutations of the *MET* gene on 7q31 have been causally associated with HPRCC, but *MET* is mutated in less than 10% of sporadic papillary renal cancers
- Families with inherited mutations in *MET* leading to multi-focal papillary renal cancer (type 1) are rarer than other inherited renal cancer syndromes, including HLRCC, Birt–Hogg–Dubé syndrome, and VHL syndrome

HEREDITARY LEIOMYOMATOSIS AND RENAL CELL CANCER (TYPE 2 PAPILLARY) – HLRCC[1]

- HLRCC is an autosomal cancer susceptibility syndrome characterized by the development of cutaneous and uterine leiomyomas and renal cancer, most commonly papillary type 2 renal cancer
- HLRCC tends to have an early age of onset (mean 40 years), be high grade, and have an aggressive course. Cells associated with HLRCC have distinctive pathological features
- In *FM*-mutant renal cancers, fumarate inhibits HIF proline hydroxylases, allowing for HIF accumulation and increased HIF-mediated transcription. This leads to transcription of downstream targets, including a family of histone-regulating demethylases and loss of Nrf2-dependent activation of antioxidant pathways through KEAP1 modification

HIF, hypoxia-inducible factor. HLRCC, hereditary leiomyomatosis renal cell cancer; HPRCC, hereditary papillary renal cell carcinoma; MET, mesenchymal-epithelial transition; RCC, renal cell carcinoma; VHL, Von Hippel-Lindau.

1. Haas NB, Nathanson KL. Adv Chronic Kidney Dis. 2014;21(1):81–90.

Birt–Hogg–Dubé syndrome[1]

Birt–Hogg–Dubé syndrome is an autosomal dominant syndrome characterized by the development of fibrofolliculomas (dysplastic hair follicles), lung cysts, spontaneous pneumothorax, and renal cancer, occurring in about

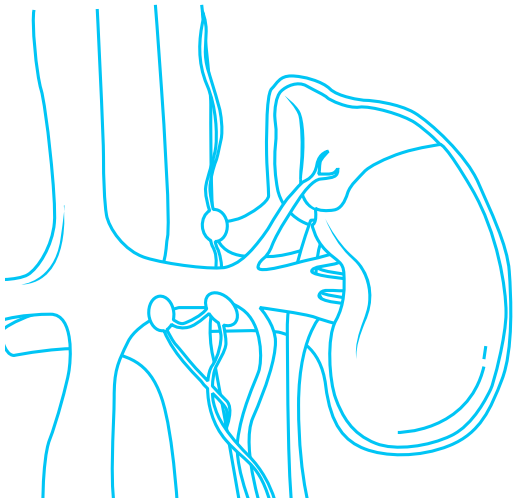
1 in 200,000
individuals

Point mutations or large genomic rearrangements of the gene *FLCN* is causative for the syndrome; however, the function of the FLCN protein is controversial

A wide spectrum of renal cancers are observed in patients with Birt–Hogg–Dubé syndrome even within the same kidney.

These include:

- pRCC
- ccRCC
- Mixed
- Oncocytomas
- **Most commonly, hybrid oncocytic tumors**



ccRCC, clear cell renal cell carcinoma; FLCN, folliculin; pRCC, papillary renal cell carcinoma.

1. Haas NB, Nathanson KL. Adv Chronic Kidney Dis. 2014;21(1):81–90.

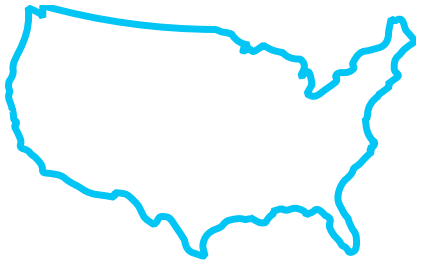
Other inherited syndromes with increased risk of renal cancer[1]

BAP1 mutations and familial renal cancer	• BAP1 mutations have been associated with a higher tumor grade and decreased overall survival • Studies have suggested that BAP1 mutations predispose to familial clear cell renal cancer, along with uveal, cutaneous melanoma, and mesothelioma[2]
Chromosome 3 translocations	• Inherited susceptibility due to balanced translocations involving chromosome 3 have been described, caused by loss of the rearranged chromosome during mitosis. • Multiple genes involved in the pathogenesis of clear cell renal cancer including *VHL*, *PBRM1*, *BAP1*, and *SETD2* are located on chromosome 3
PTEN hamartoma tumor syndrome (Cowden disease)	• Sporadic renal cancers and cell lines have shown that mutations in PTEN are present, particularly in late stage and clear cell renal cancers. ccRCC is reported more frequently in patients with Cowden disease
SDH-associated paraganglioma / pheochromocytoma	• Mutations in three of the four proteins (SDHB/C/D) comprising the succinate dehydrogenase complex, have been associated with an increased risk of renal cancer, including clear cell, chromophobe, and oncocytomas
Tuberous sclerosis complex	• An autosomal dominant genetic disorder characterized by the formation of hamartomas in multiple organs, including the brain, kidney, skin, and lungs

BAP1, BRCA1-associated protein 1; PBRM1, polybromo 1; SDH, succinate dehydrogenase; SETD2, SET Domain Containing 2; VHL, Von Hippel-Lindau.

1. Haas NB, Nathanson KL. Adv Chronic Kidney Dis. 2014;21(1):81–90. 2. Walpole S, et al. J Natl Cancer Inst. 2018;(12):1328–41.

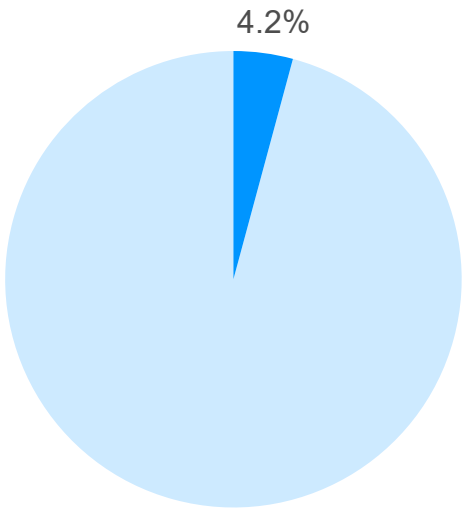
Incidence and prevalence



In the United States,

~81,800

new cases of kidney and renal pelvis cancer
were estimated for 2023[1,*]

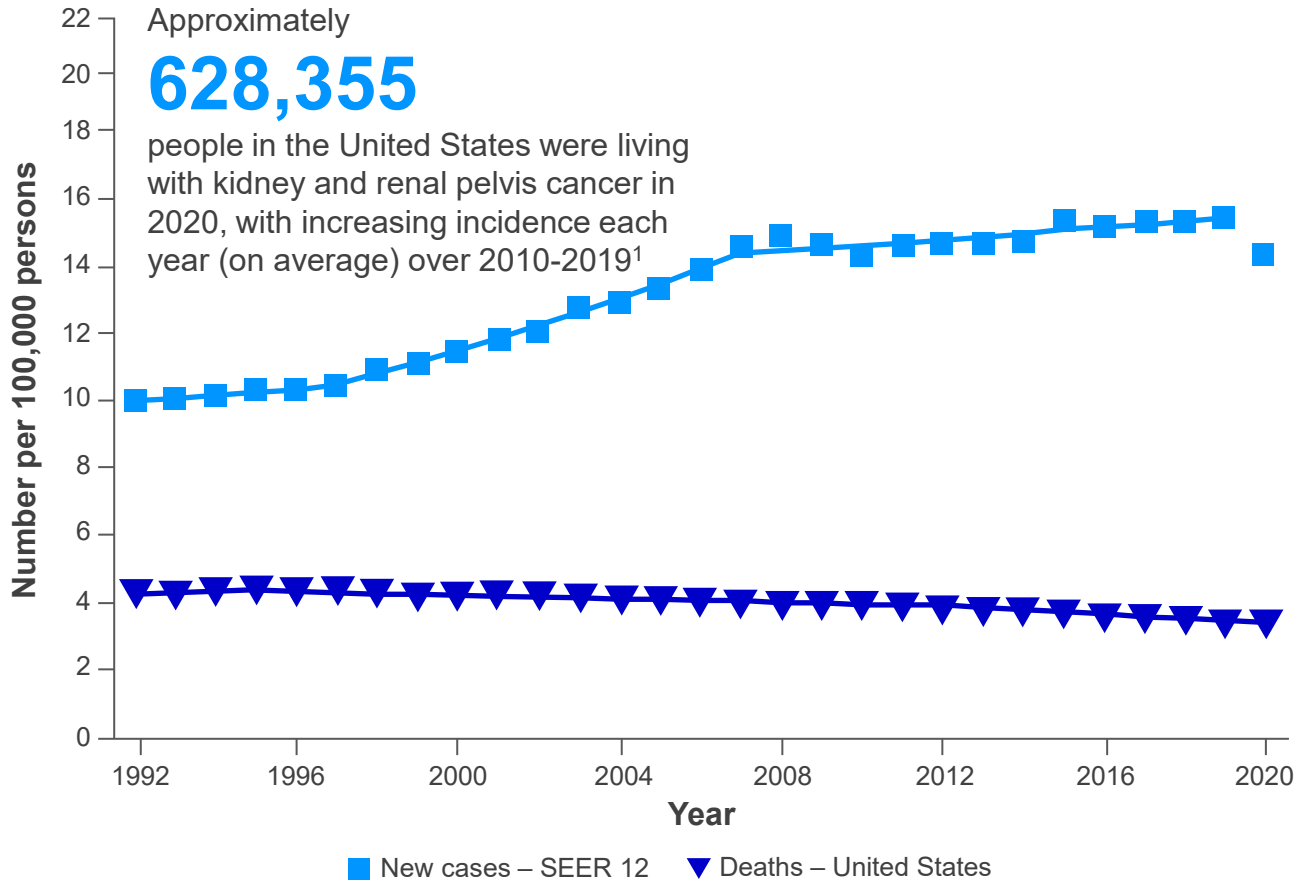


Kidney and renal pelvis cancer represents

4.2%

of all new cancer cases in the United States

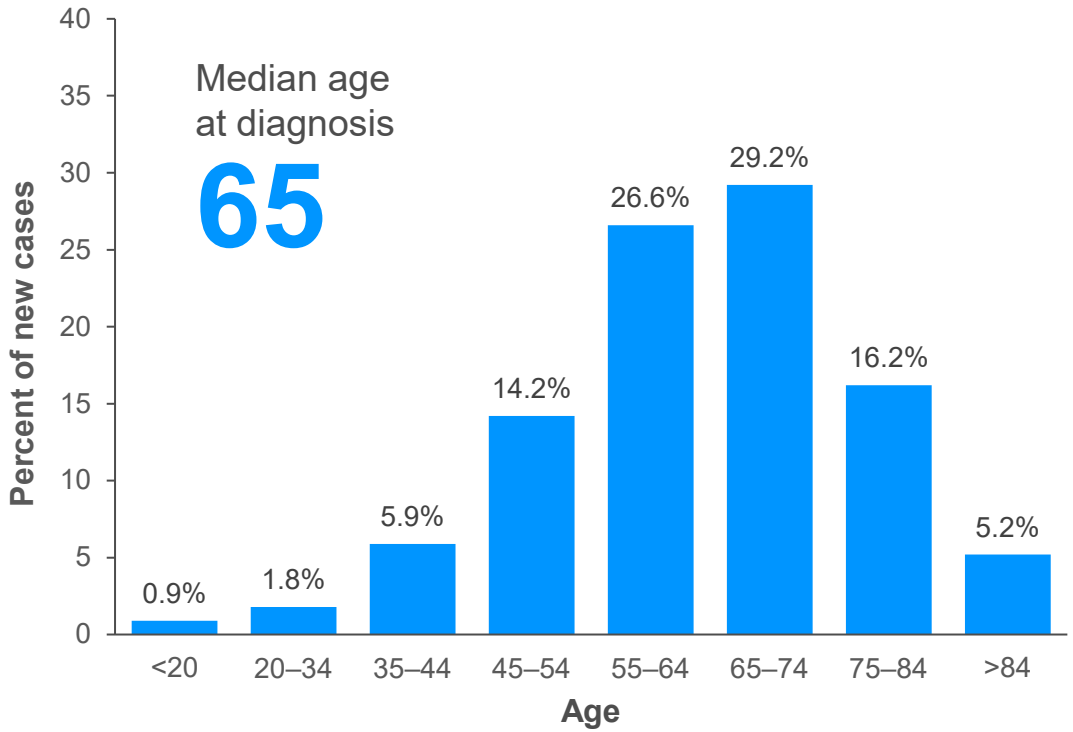
CHANGE IN INCIDENCE AND DEATH RATES PER 100,000 PERSONS OVER TIME IN THE UNITED STATES[1,*]



*New cases derived from SEER 12. Deaths derived from US Mortality. All Races, Both Sexes. Rates are Age-Adjusted.
1. SEER Stat Fact Sheets: Kidney and Renal Pelvis Cancer. https://seer.cancer.gov/statfacts/html/kidrp.html (accessed 30 June 2023).

Incidence by age and demographics

KIDNEY AND RENAL PELVIS CANCER ARE MOST FREQUENTLY DIAGNOSED AMONG PEOPLE AGED 65–74[1,*]



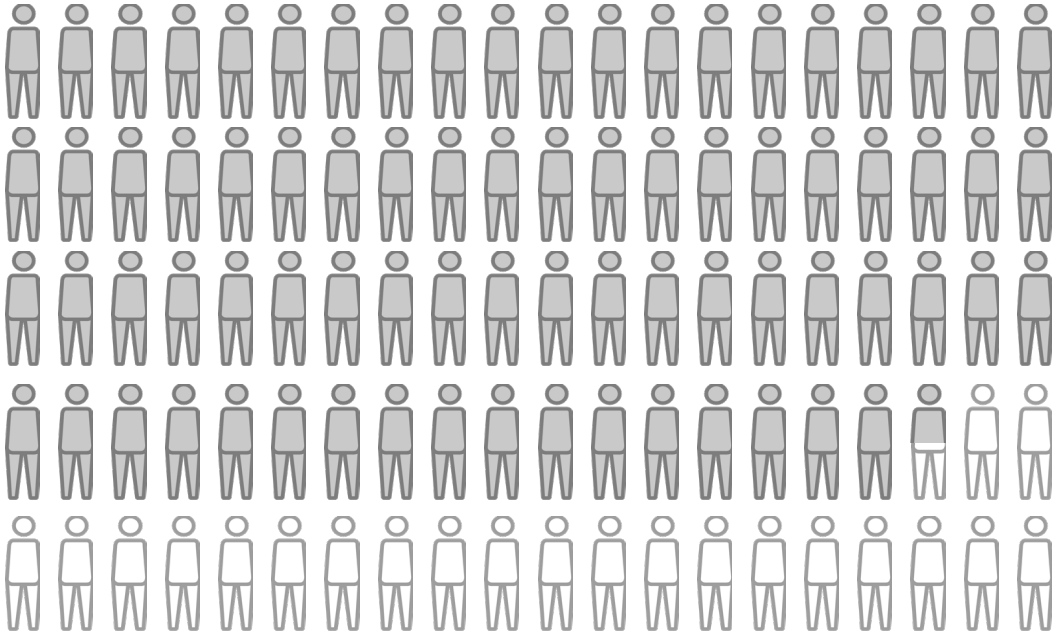
NUMBER OF NEW CASES PER 100,000 PERSONS BY RACE/ETHNICITY AND SEX: KIDNEY AND RENAL PELVIS CANCER[1,†]

	Males	Females
All races	23.5	11.7
Non-Hispanic White	24.2	11.7
Non-Hispanic Black	25.7	13.0
Non-Hispanic Asian/Pacific Islander	12.1	5.7
Non-Hispanic American Indian/Alaska Native	37.7	18.3
Hispanic	23.9	13.7

*SEER 22 2016-2020, All Races, Both Sexes. †SEER 22 2016–2020, Age-Adjusted.

1. SEER Stat Fact Sheets: Kidney and Renal Pelvis Cancer. https://seer.cancer.gov/statfacts/html/kidrp.html (accessed 30 June 2023).

Relative survival



5-Year Relative Survival (All Stages Combined)*,†

77.6%

NUMBER OF DEATHS PER 100,000 PERSONS BY RACE/ETHNICITY AND SEX: KIDNEY AND RENAL PELVIS CANCER[1,‡]

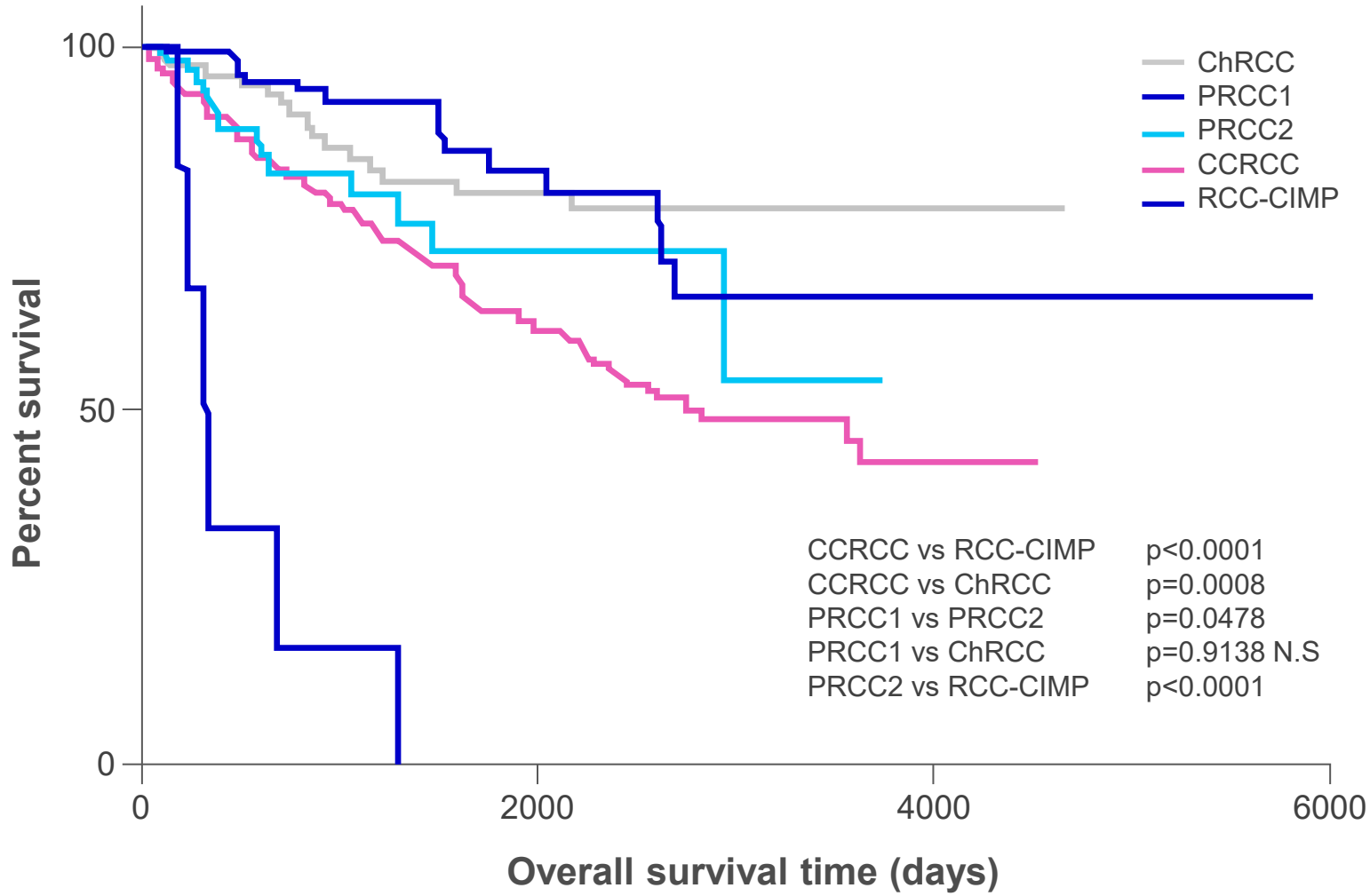
	Males	Females
All races	5.1	2.2
Non-Hispanic White	5.3	2.3
Non-Hispanic Black	5.2	2.1
Non-Hispanic Asian/Pacific Islander	2.4	1.0
Non-Hispanic American Indian/Alaska Native	9.3	3.9
Hispanic	4.8	2.1

*Kidney and renal pelvis cancer. Unshaded figures represent those who have died from kidney and renal pelvis cancer. Shaded figures represent those who have survived 5 years or more.
†SEER 22 (Excluding IL/MA) 2013–2019. ‡US 2016–2020, age-adjusted.

1. SEER Stat Fact Sheets: Kidney and Renal Pelvis Cancer. https://seer.cancer.gov/statfacts/html/kidrp.html (accessed 30 June 2023).

Survival by subtype

- The TCGA assessed survival in 894 patients with RCC.[1] Patients with ccRCC and with the RCC-CIMP subtype of pRCC were reported to have the worst survival[1]
- In another clinical study, recurrence post partial nephrectomy also varied by subtype, with ccRCC having the highest rate of recurrence as compared to chRCC or pRCC[2]

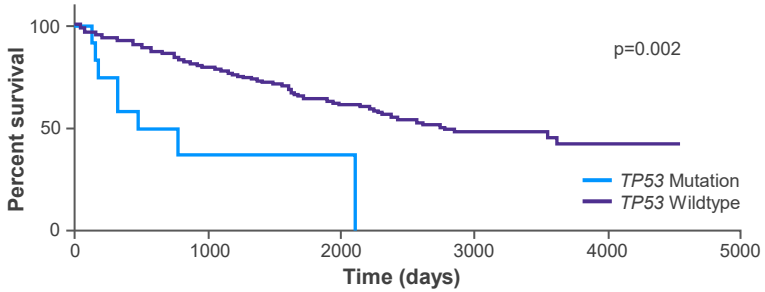


ccRCC, clear cell renal carcinoma; chRCC, chromophobe renal cell carcinoma; pRCC, papillary renal cell carcinoma; RCC-CIMP, CpG island methylator phenotype renal cell carcinoma; TCGA, The Cancer Genome Atlas.

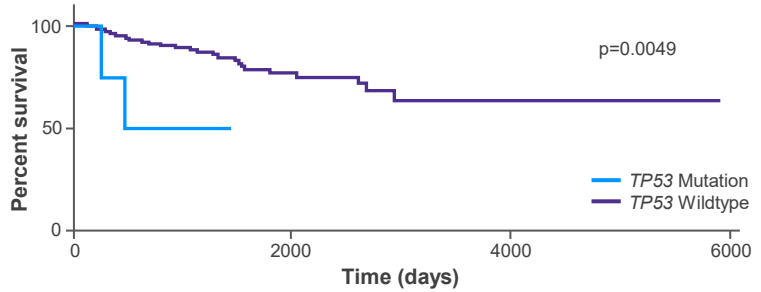
1. Ricketts CJ, et al. Cell Reports. 2018;23:313–26; 2. Nguyen DP, et al. Urol Oncol. 2016;34(6):259.e1–8.

Survival and mutation status

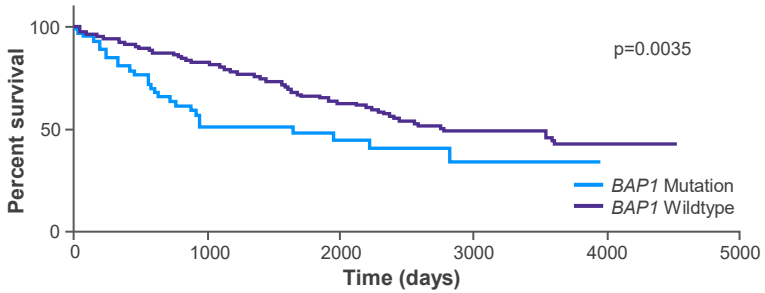
ccRCC *TP53* MUTATION



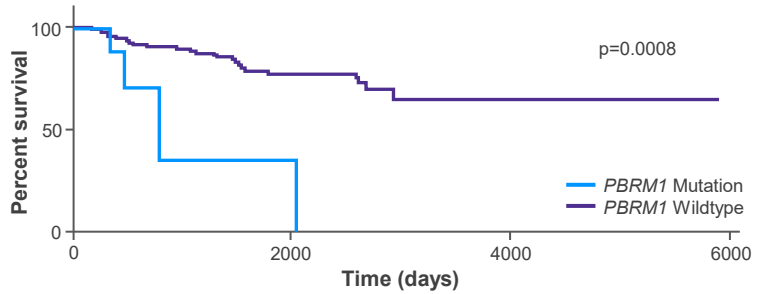
PRCC *TP53* MUTATION



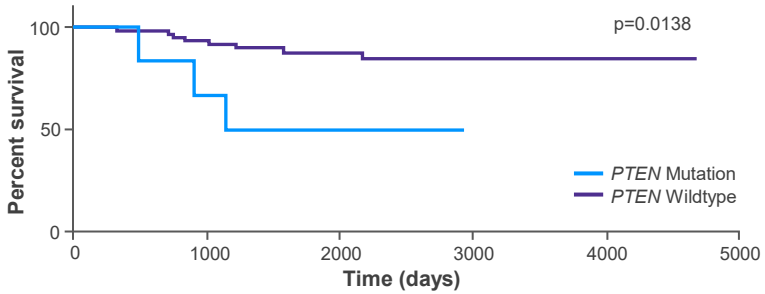
ccRCC *BAP1* MUTATION



PRCC *PBRM1* MUTATION



ChRCC *PTEN* MUTATION



- The overall mutation rate has been suggested to be higher for ccRCC and pRCC as compared to chRCC, with pRCC having the highest overall mutation rate[1]
- Common mutations associated with poor survival were *TP53*, *PTEN*, *BAP1*, *PBRM1*, and *CDKN2A*[1]
- Mutations and gene alterations have also been observed in pathways commonly altered in cancer, specifically the Hippo (pRCC, ccRCC) and Wnt (pRCC, ccRCC, chRCC) signaling pathways, as well as in the PI3K/AKT pathway (all subtypes)[1]

BAP1, BRCA1-associated protein 1; ccRCC, clear cell renal cell carcinoma; *CDKN2A*, cyclin-dependent kinase inhibitor 2A; chRCC, chromophobe renal cell carcinoma; *PBRM1*, polybromo 1; pRCC, papillary renal cell carcinoma; *PTEN*, phosphate and tensin homolog; *TP53*, tumor protein p53.

1. Ricketts CJ, et al. Cell Reports. 2018;23:313–26.

Prognostic measures

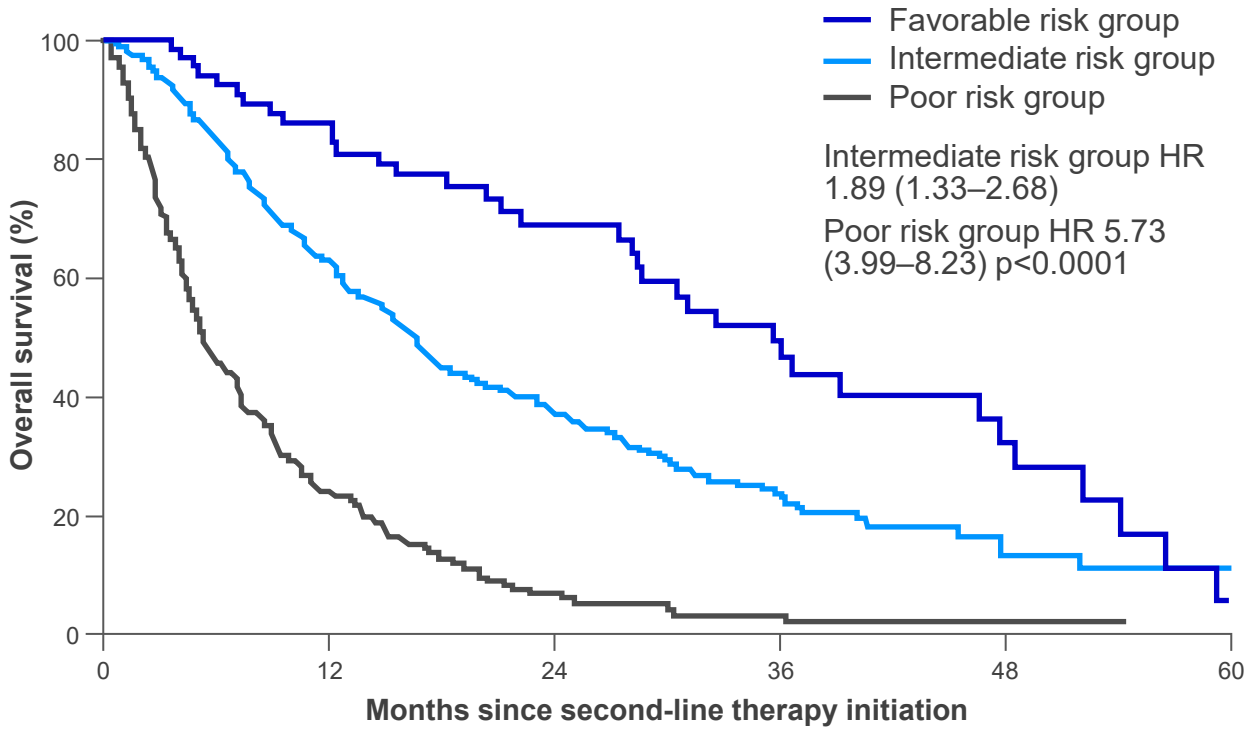
THE INTERNATIONAL mRCC CARCINOMA DATABASE CONSORTIUM MODEL (IMDC) FOR PROGNOSIS IN FIRST-LINE TREATMENT FOR mRCC

Criteria

- Karnofsky performance status <80%
- Time from diagnosis to treatment <1 year
- Hemoglobin < LLN
- Calcium concentration > ULN
- Neutrophils > ULN
- Platelets > ULN

Number of criteria	Group	Median overall survival
0	Favorable	35.3 months (95% CI 28.3–47.8)
1–2	Intermediate	16.6 months (95% CI 14.9–17.9)
3–6	Poor	5.4 months (95% CI 4.7–6.8)

OVERALL SURVIVAL ACCORDING TO THE IMDC MODEL[1]



Patients who received second-line targeted therapy after progressing on first-line targeted therapy for mRCC were included in the study. Patients who had immunotherapy before their first targeted therapy were included.[1]

CI, confidence interval; HR, hazard ratio; IMDC, International mRCC Database Consortium; LLN, lower limit of normal; mRCC, metastatic renal cell carcinoma; ULN, upper limit of normal.

1. Ko JJ, et al. Lancet Oncol. 2015;16(3):293–300.