

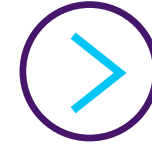


Renal Cell Carcinoma

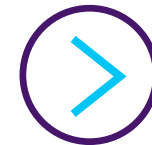
Disease State

Content

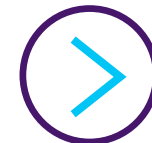
TUMOR BIOLOGY AND PATHOGENESIS



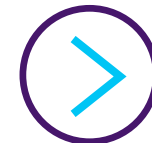
NATURAL HISTORY AND PROGRESSION



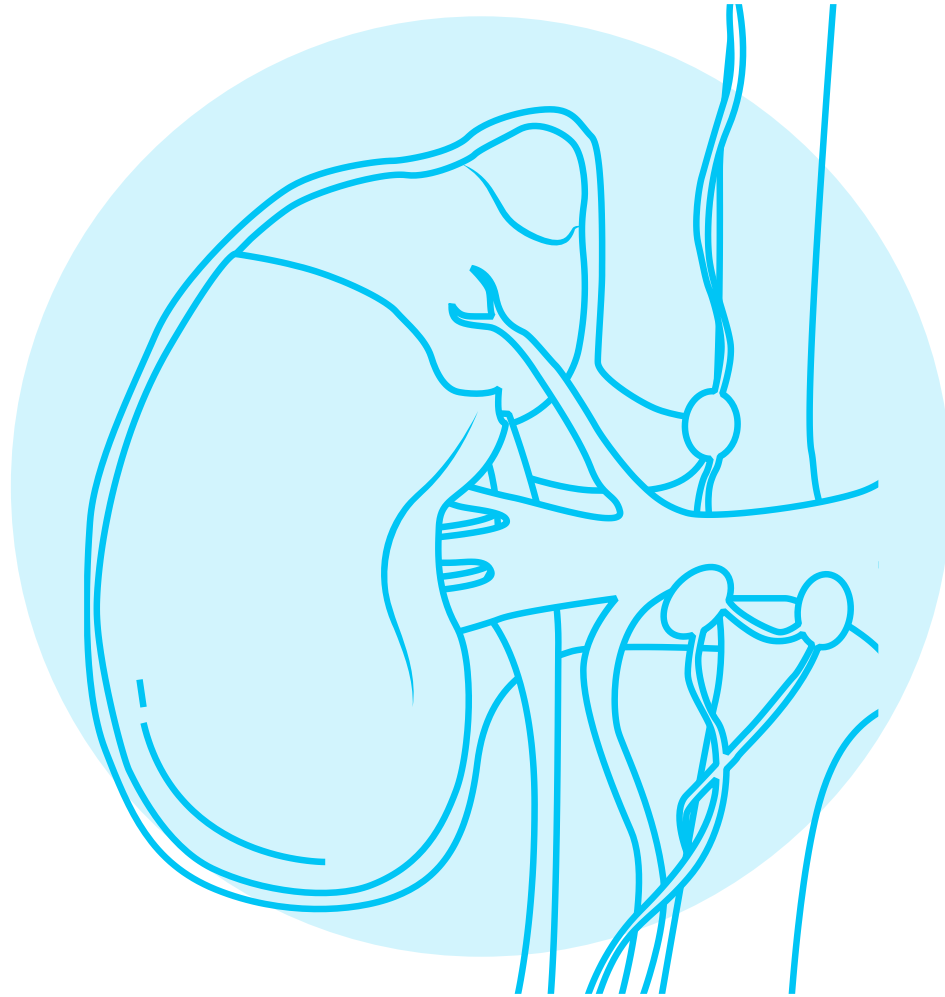
RISK FACTORS AND DISEASE STRATIFICATION



INCIDENCE, PREVALENCE, AND SURVIVAL



RCC subtypes

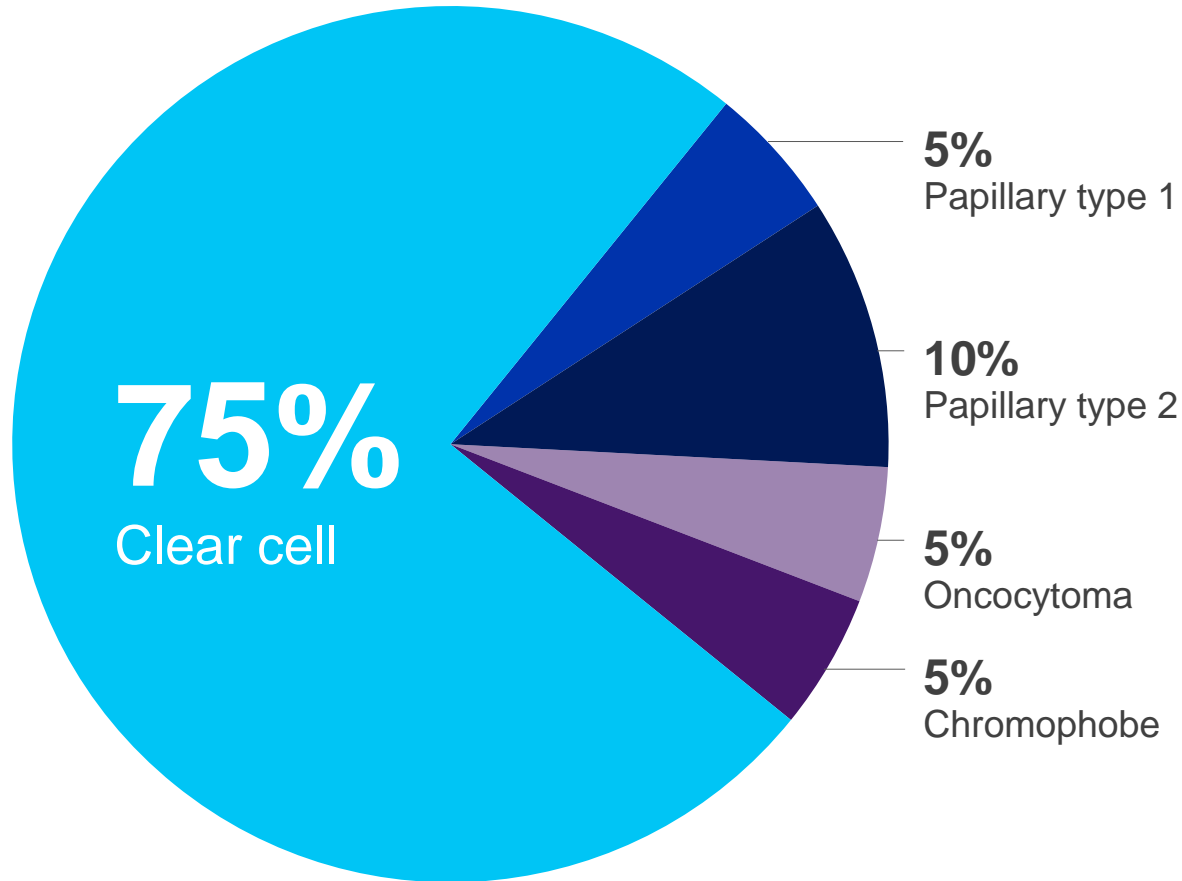


- RCC arises from the renal epithelium, representing >90% of renal malignancies.¹ RCC is composed of several different subtypes, which differ in several ways¹
 - Major subtypes (4% incidence) include clear cell RCC (ccRCC), papillary RCC (pRCC), chromophobe RCC (chRCC)¹
 - Unclassified RCC (uRCC)¹
 - Other subtypes are very rare, each with $\leq 1\%$ total incidence¹
 - 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 pRCC²
- There is significant intra- and intertumor heterogeneity in ccRCC, which could contribute to observed heterogeneous clinical outcomes¹

Most common RCC subtypes



INCIDENCE (%)^{1,2}

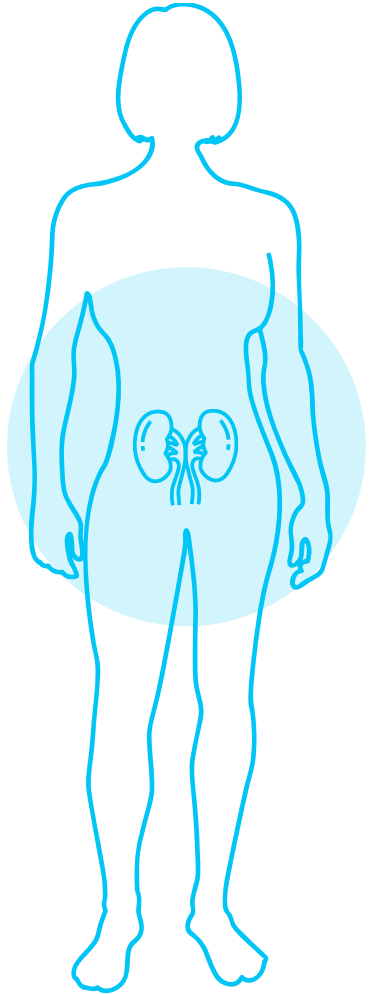


- RCC is a heterogeneous group of diseases¹
- Of all kidney tumors, >90% are RCC¹
- Different neoplasms of the kidney are characterized by distinct histologies, genetic alterations, clinical course, and response to therapy^{1,2}

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; <i>SETD2</i> , <i>BAP1</i> , and <i>MTOR</i> 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 <i>FLCN</i> 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 <i>TP53</i> and <i>PTEN</i> ; imbalanced chromosome duplication; high TERT expression by DNA rearrangement within the TERT promoter region with kataegis



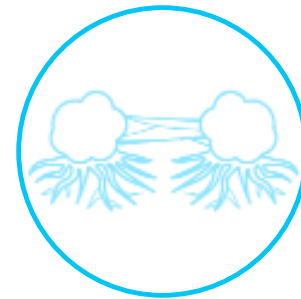
Approximately
30%

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 evident¹

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 understood⁴

Key mutations in ccRCC



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

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 subtypes¹
- RCC subtypes have also shown different transcriptional programs²

Tumor heterogeneity overview¹

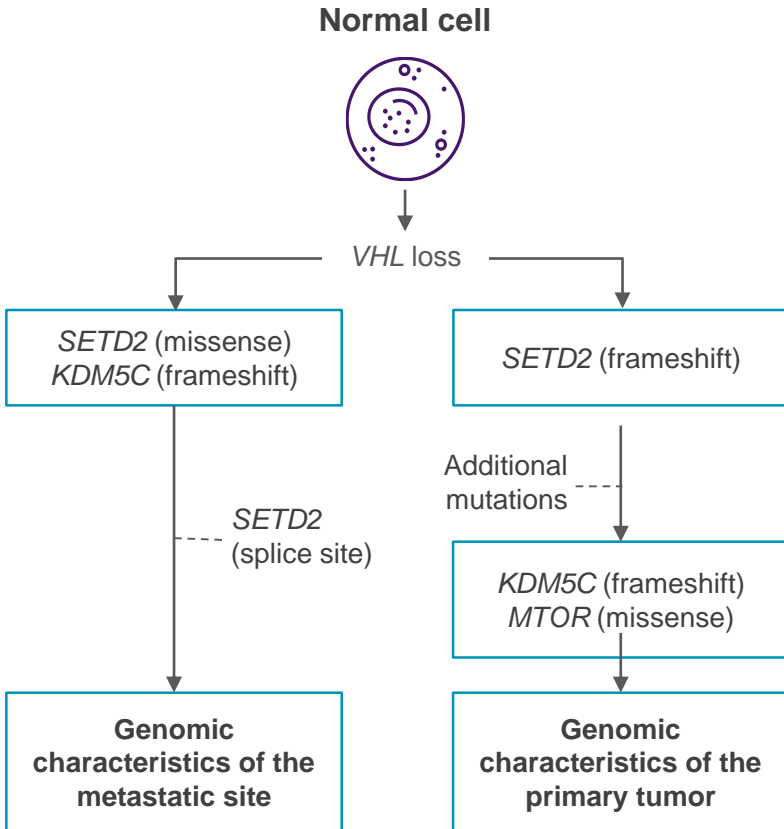


- Tumor temporal and spatial heterogeneity is believed to be due to genetic instability, allowing for genomic alterations as the tumor grows and develops
- Mutations occurring subsequent to the most recent common ancestor (MRCA) promote subclone formation and evolution

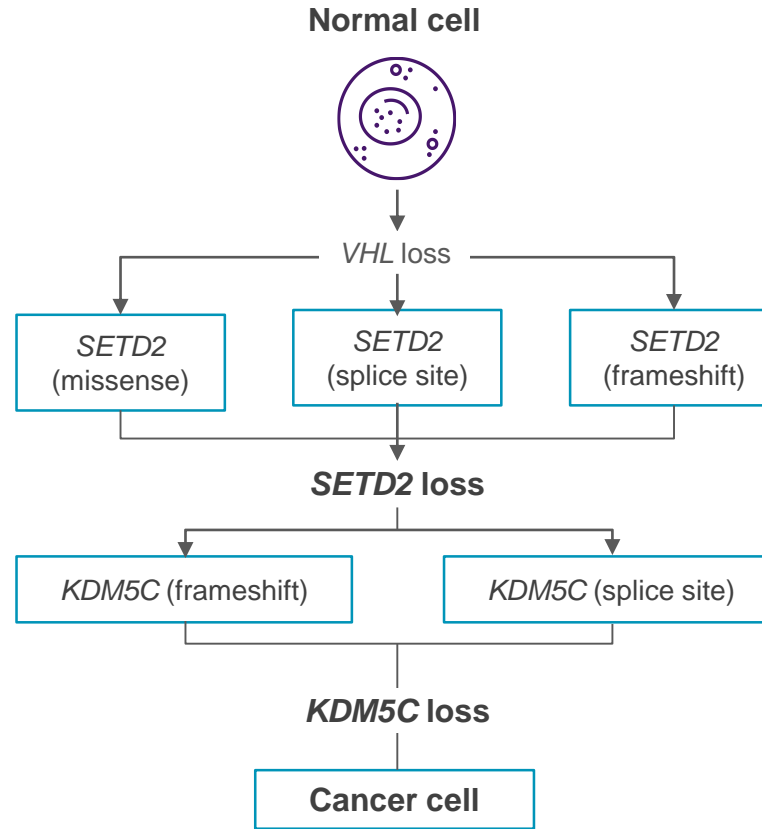
Tumor heterogeneity at the mutation level



PHYLOGENETIC TREE MODEL



BRAIDED RIVER MODEL



- 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

Phylogenetic tree showing tumor divergence with different mutations across subclones

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

RCC Pathogenesis

Biomarkers



- Unlike other cancers, RCC does not carry a high mutational load; analysis by MSKCC Score suggested no trend with stratification by risk group¹
- No differences in expression of T cell effector molecules (granzyme A and perforin) or checkpoint expression were observed by MSKCC risk group²

PROGNOSTIC AND PREDICTIVE BIOMARKERS IN RCC¹

Biomarker	Association	Biomarker	Association
Gene alterations in <i>BAP1</i>	Worse overall survival	Negative IHC expression for <i>BAP1</i>	Better mTOR inhibitor response
Gene alterations in <i>PBRM1</i>	Better overall survival		
<i>PBRM1</i> wild type + gene alterations <i>BAP1</i>	Worse overall survival	Negative IHC expression for <i>PBRM1</i>	Better mTOR inhibitor response
Gene alterations in <i>KDM5C</i>	Better overall survival		
<i>PDCD1</i> , <i>CTLA4</i> and <i>TLR9</i>	Worse overall survival	<i>SETD2</i> , <i>TP53</i> , and <i>VHL</i>	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 evasion²
- 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 metabolism³
- 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 pRCC⁴
- 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 ccRCC⁵
- Changes in the tryptophan pathway have also been observed, including increased levels of the immunosuppressive metabolite kynurenine⁵
- Some studies report additional metabolic changes with tumor grade, suggesting a metabolic shift with progression^{5,6}

Immune engagement



- Numerous studies have explored the interaction between the immune system and RCC¹⁻⁹
- 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 stage⁷
- 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}

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

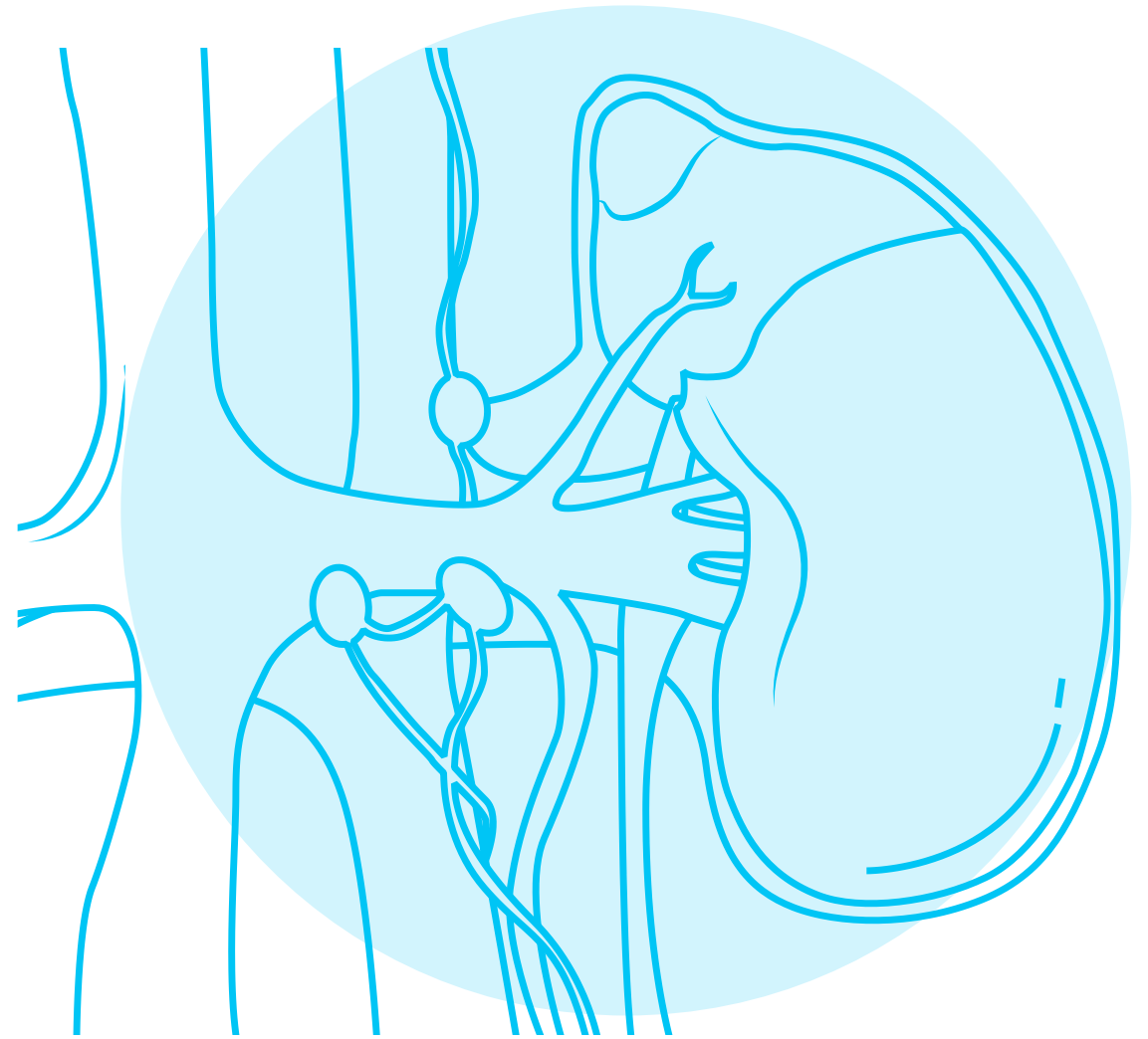
Signs and symptoms



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 INCLUDE¹:

- 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



RCC Natural History and Progression

Diagnosis¹



- >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

Disease classification – grade and stage



Staging of RCC is based on size, position, and lymph node involvement, and treatment is largely guided by stage¹

STAGE I

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

Management options

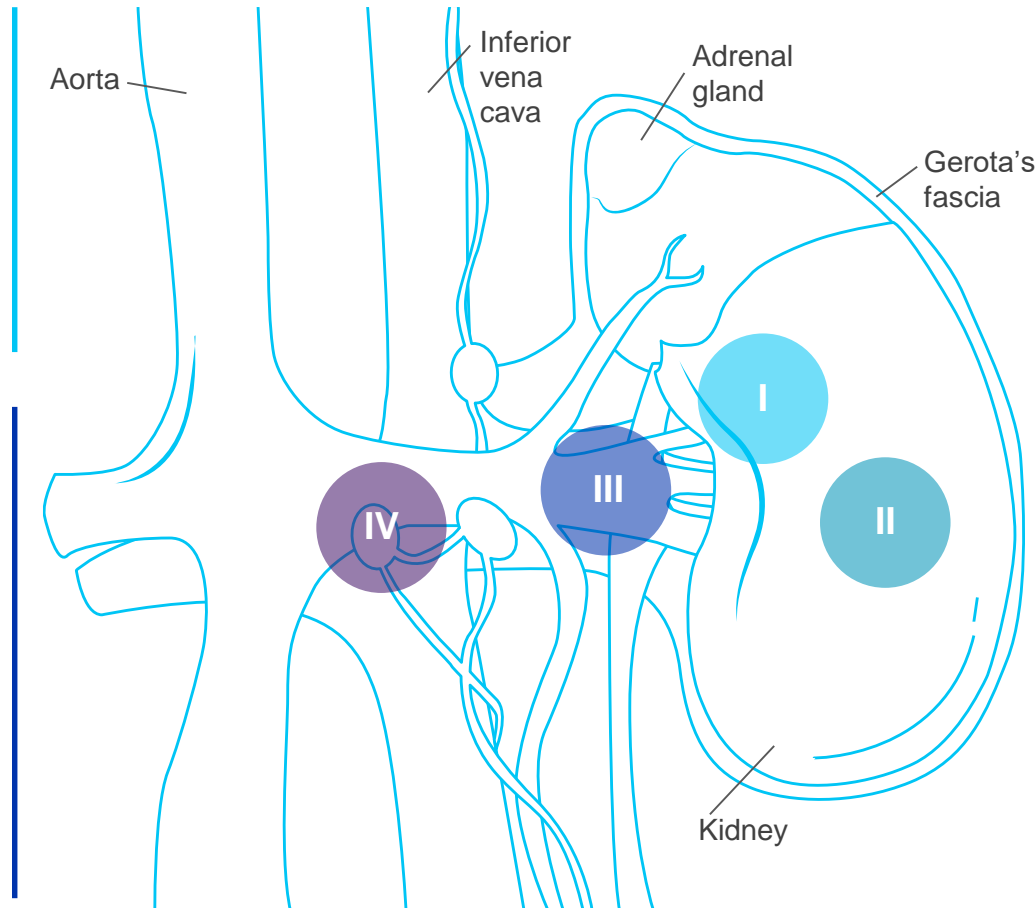
- Partial nephrectomy
- If not technically feasible, active surveillance or ablative therapies in selected patients with small masses

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
- Distant metastases
- 5-year survival rate of 20%

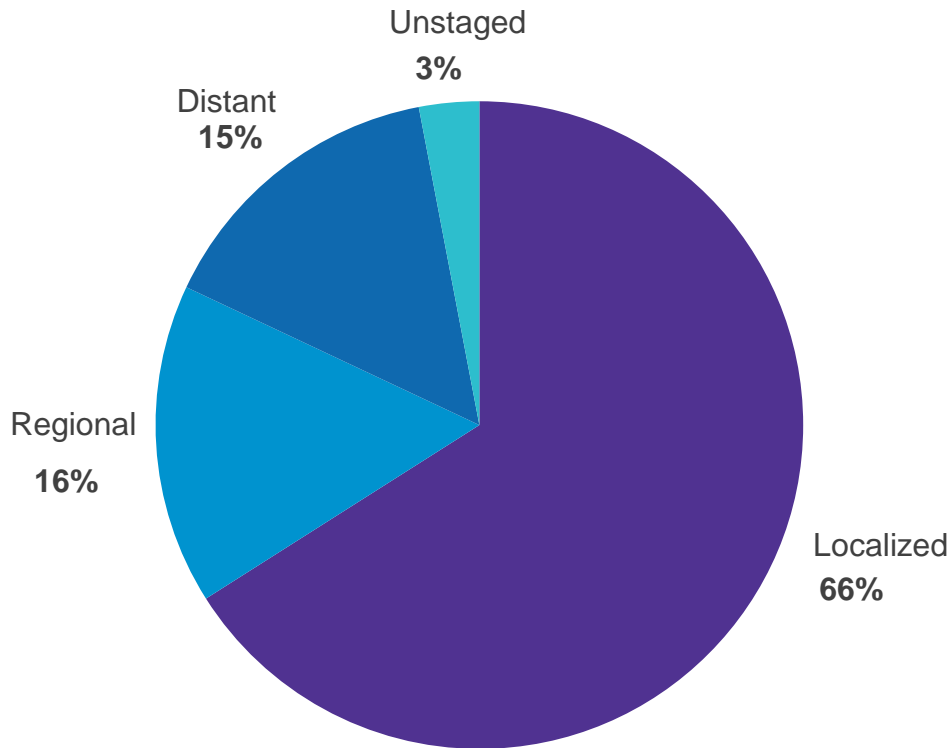
Management options

- 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

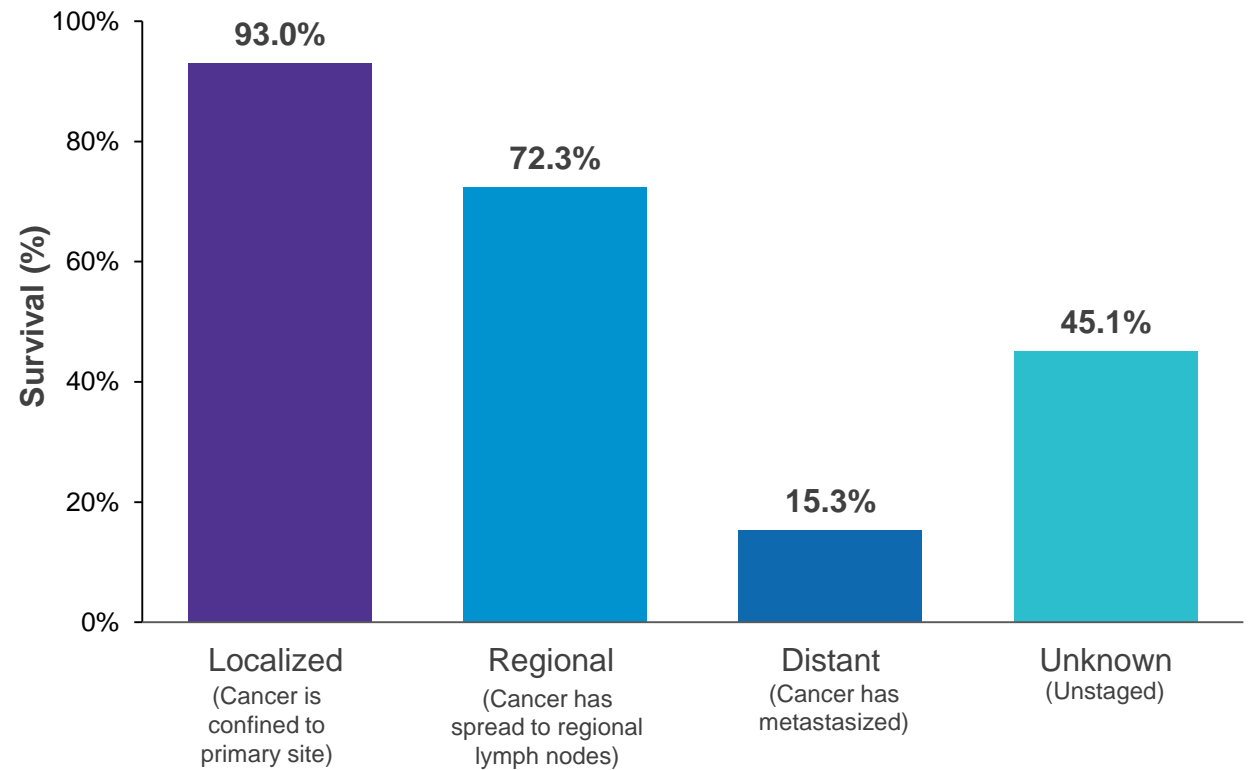


Stage at diagnosis of kidney and renal pelvis cancer is linked with survival¹

PROPORTION OF PATIENTS WITH DIFFERENT DISEASE STAGES AT DIAGNOSIS^{1,*}



5-YEAR RELATIVE SURVIVAL VARIES ACCORDING TO DISEASE STAGE AT DIAGNOSIS^{1,*}



*SEER 17 2012–2018, 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 October 2022).

Risk factors for RCC incidence



Non-modifiable¹⁻³

- 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 Risk Factors and Disease Stratification

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



AGE²

The median age of people at diagnosis is 65 years



GENDER

RCC is twice as common in men as in women



RACE²

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



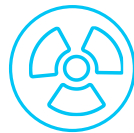
HIGH BLOOD PRESSURE

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



Hereditary syndromes associated with RCC1

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

Genetic and hereditary risk factors



THE FOUR MAJOR, AUTOSOMAL-DOMINANT, HERITABLE RCC SYNDROMES RECOGNIZED BY THE NATIONAL CANCER INSTITUTE¹

Syndrome	Gene locus, gene type (protein)	Renal tumor pathology type	Non-renal tumors and associated abnormalities	Cumulative lifetime cancer risk
Von Hippel-Lindau (VHL) syndrome¹	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 carcinoma¹	MET 7q34, proto-oncogene (hepatocyte growth factor receptor)	Papillary type 1	None known	Approaching 100%
Birt-Hogg-Dubé syndrome¹	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 RCC¹	FH 1q42.1, tumor suppressor (fumarate hydratase)	'HLRCC-type RCC' may be new entity (formerly called papillary type 2)	Cutaneous leiomyomas, uterine leiomyomas (fibroids)	Up to 32%

These pathogenic variants are estimated to account for

5–8%
of RCC cases²



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 Kidney Cancer. National Cancer Institute website. https://www.cancer.gov/types/kidney/hp/kidney-genetics-pdq#section/_24 (accessed October 2022); 2. Genetics of Kidney Cancer. National Cancer Institute website. https://www.cancer.gov/types/kidney/hp/kidney-genetics-pdq#section/_2946 (accessed October 2022).

RCC Risk Factors and Disease Stratification

Von Hippel-Lindau (VHL)



- VHL regulates the stability of HIF-1 α and HIF-2 α , transcription factors that increase expression of proangiogenic genes in response to hypoxia (ie, *VEGF*), a common state experienced by tumors which limits their growth¹
- Loss of function *VHL* mutations allow for HIF stabilization and accordingly increased HIF-mediated transcription, leading to several outcomes, including angiogenesis and tumor survival¹
- 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 tumors²
- 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 ccRCC²
- VEGF signaling has been linked to immune suppression^{3,4}

HPRCC and HLRCC



HEREDITARY PAPILLARY RENAL CELL CARCINOMA (TYPE 1 PAPILLARY) – HPRCC¹

- 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) – HLRCC¹

- 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

Birt–Hogg–Dubé syndrome¹



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**



Other inherited syndromes with increased risk of renal cancer¹



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 mesothelioma²

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

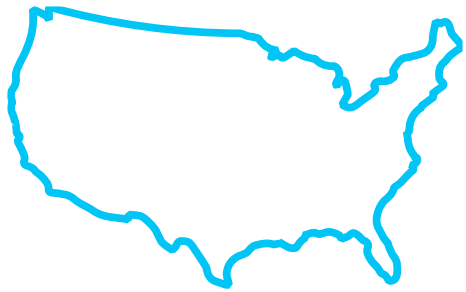
- Mutations in three of the four proteins (SDHB/C/D) comprising the succinate dehydrogenase complex, have been associated with an increased risk of renal cancer, including clear cell, chromophobe, and oncocytomas

Tuberous sclerosis complex

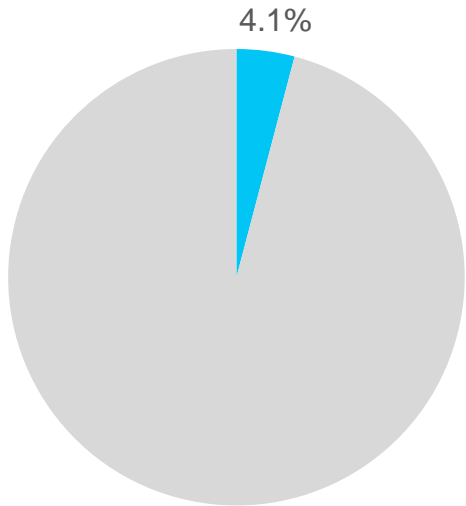
- An autosomal dominant genetic disorder characterized by the formation of hamartomas in multiple organs, including the brain, kidney, skin, and lungs



Incidence and prevalence

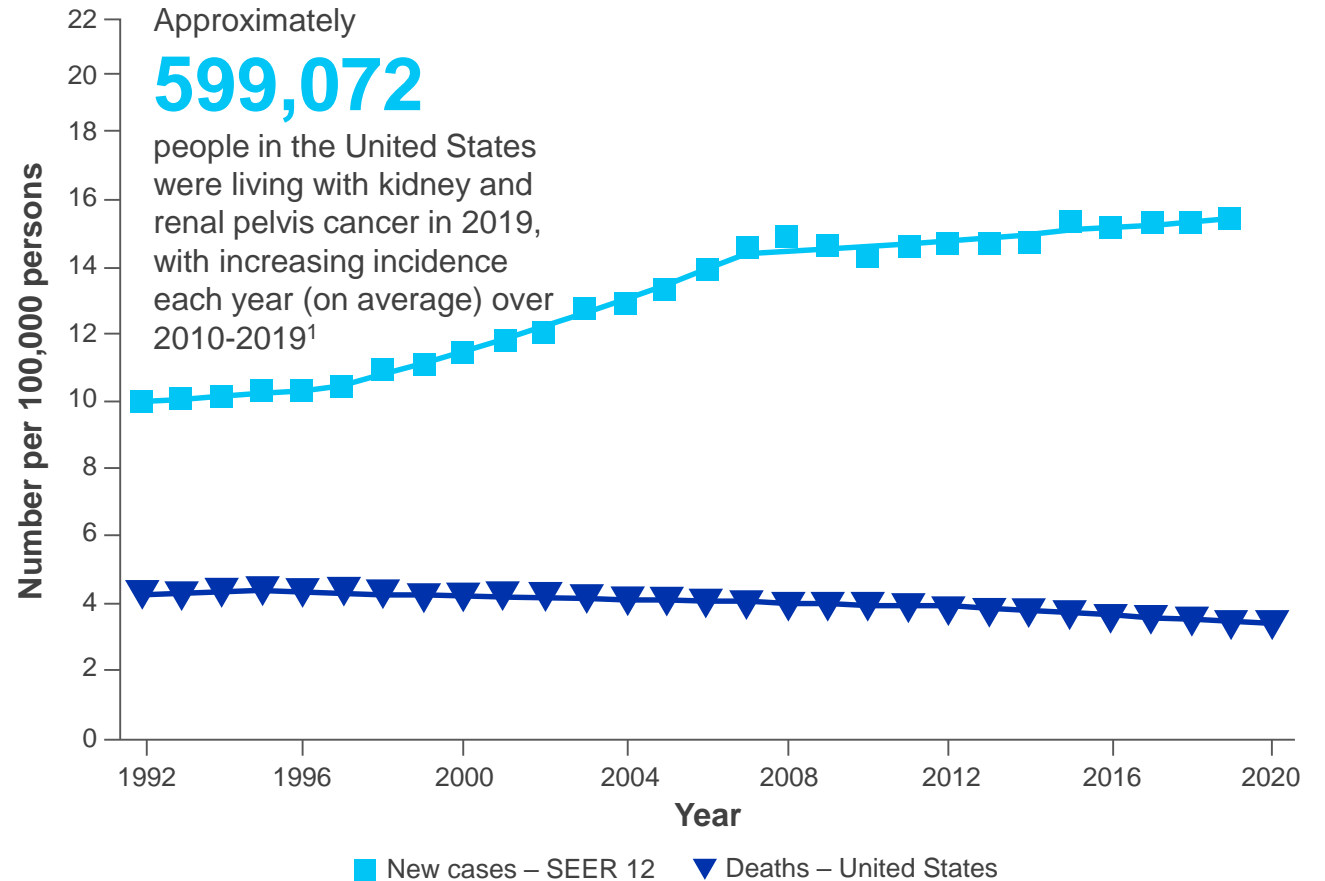


In the United States,
~79,000
new cases of kidney and renal pelvis cancer were estimated for 2022^{1,*}



Kidney and renal pelvis cancer represents
4.1%
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,*}

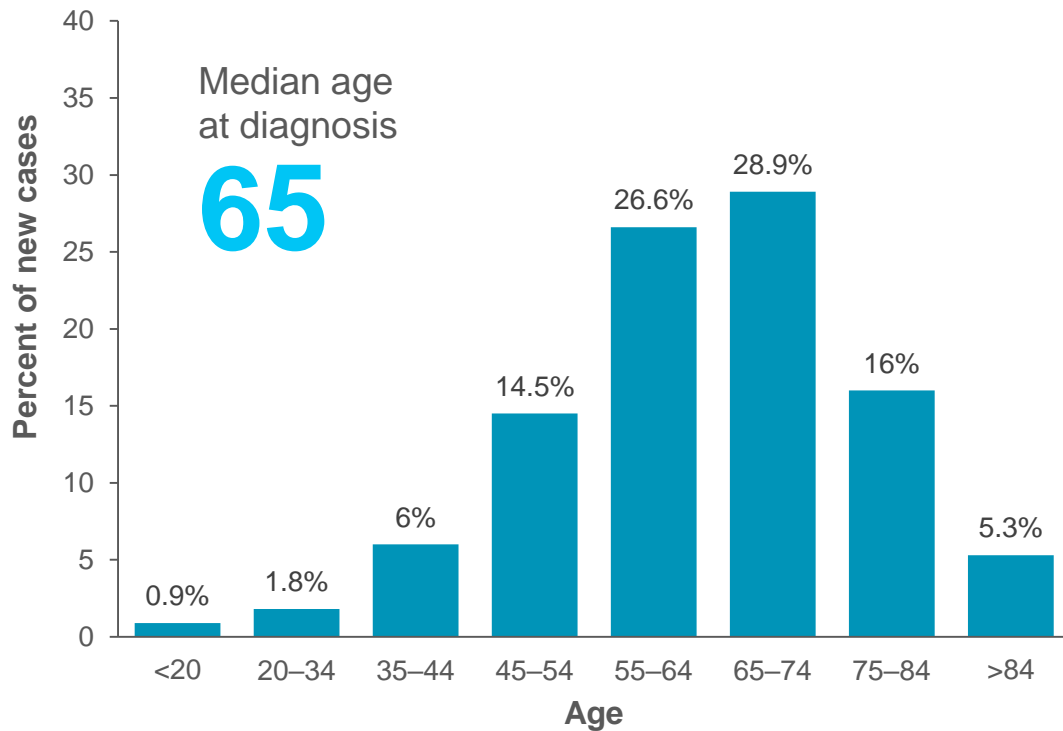


^{*}New cases derived from SEER 12. Deaths derived from US Mortality. All races, both sexes, age-adjusted.
¹. SEER Stat Fact Sheets: Kidney and Renal Pelvis Cancer. <https://seer.cancer.gov/statfacts/html/kidrp.html> (accessed October 2022).



Incidence by age and demographics

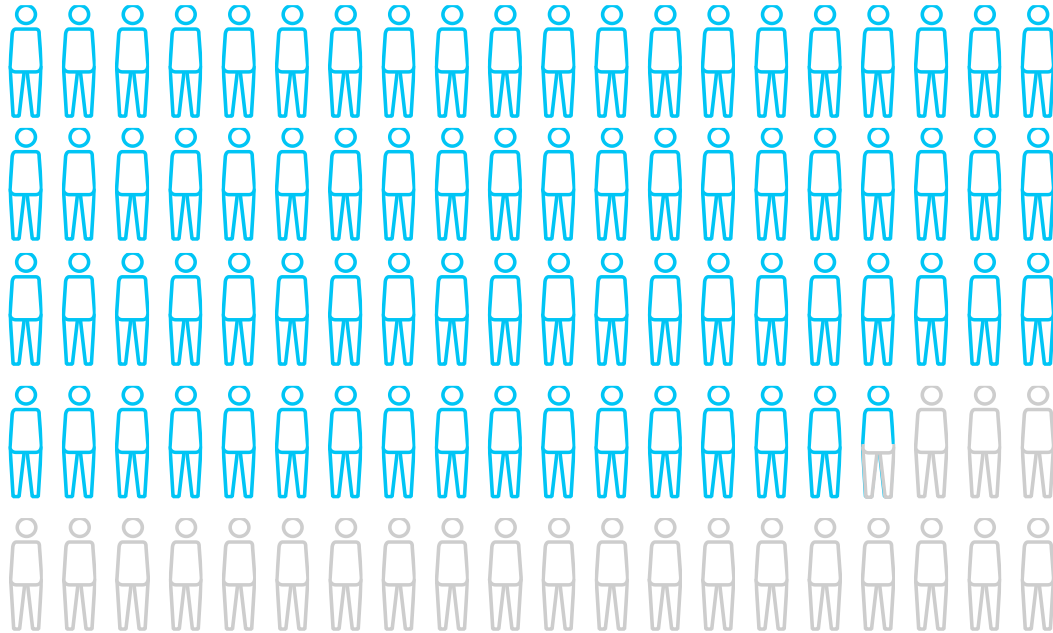
KIDNEY AND RENAL PELVIS CANCER ARE MOST FREQUENTLY DIAGNOSED AMONG PEOPLE AGED 65–74^{1,*}



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

	Males	Females
All races	23.6	11.9
Non-Hispanic White	24.3	11.9
Non-Hispanic Black	26.2	13.2
Non-Hispanic Asian/Pacific Islander	12.3	5.8
Non-Hispanic American Indian/Alaska Native	36.2	18.6
Hispanic	24.1	13.9

Relative survival



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

76.5%

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

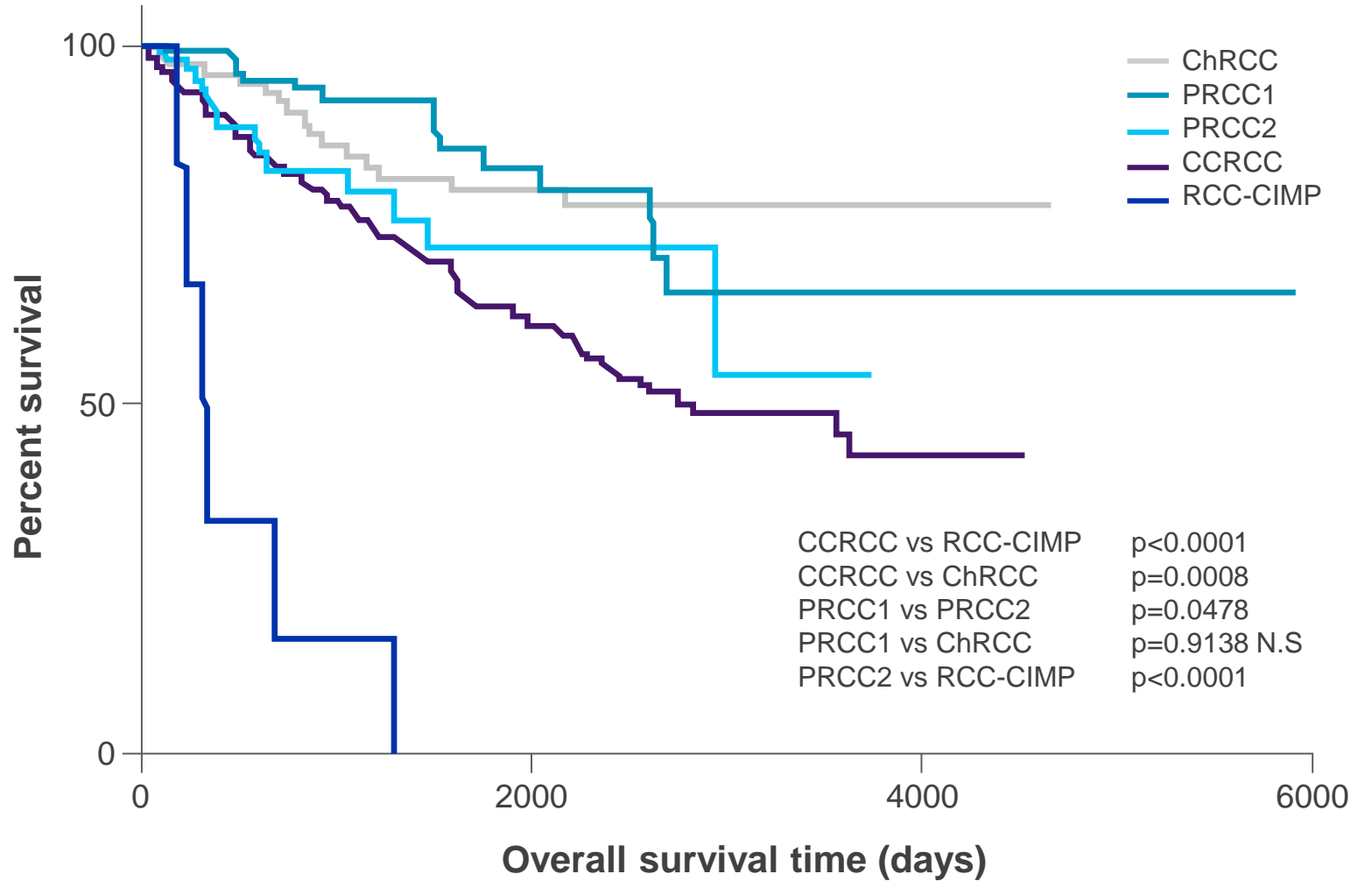
*Kidney and renal pelvis cancer. †SEER 17 2012-2018. ‡US 2016-2020, age-adjusted.

1. SEER Stat Fact Sheets: Kidney and Renal Pelvis Cancer. <https://seer.cancer.gov/statfacts/html/kidrp.html> (accessed October 2022).

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 survival¹
- 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 pRCC²

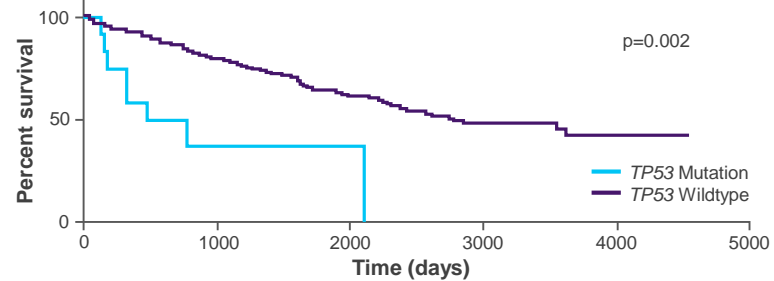


RCC Survival

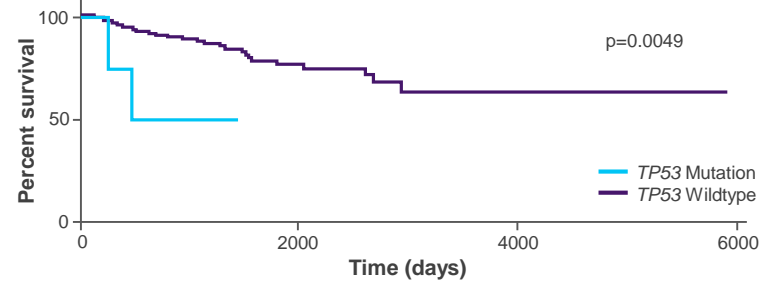
Survival and mutation status



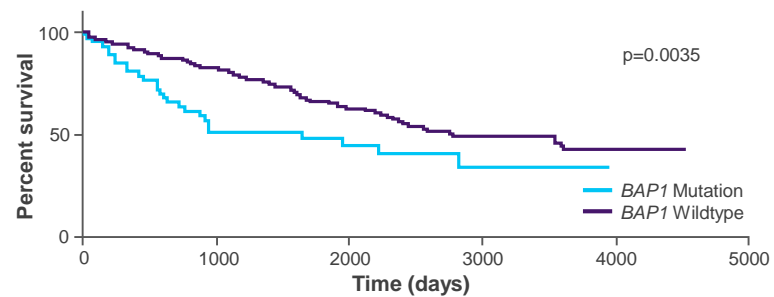
ccRCC *TP53* MUTATION



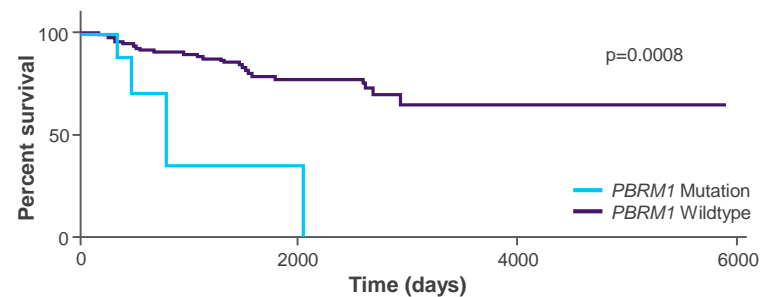
pRCC *TP53* MUTATION



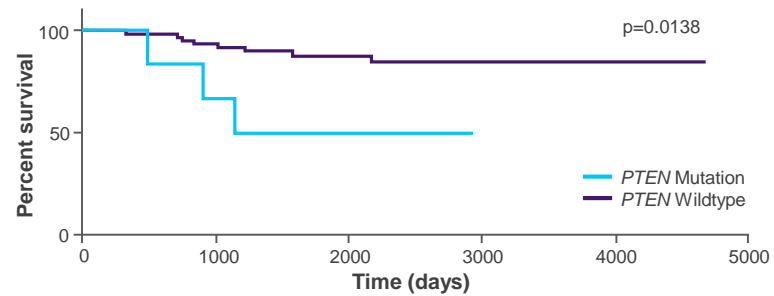
ccRCC *BAP1* MUTATION



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 rate¹
- 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

Prognostic measures



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

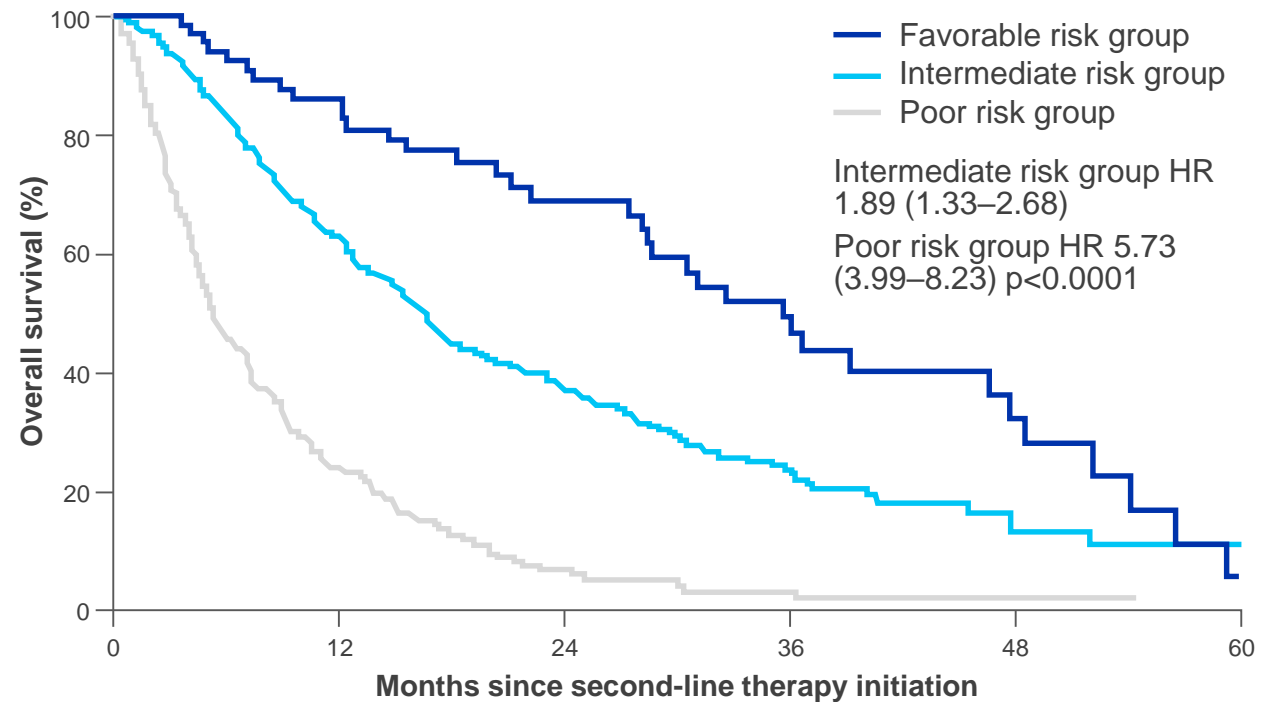
Criteria

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

Number of criteria

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 MODEL¹



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