به نام خداوند جان و خرد

Renal Cell Carcinoma For The Nephrologist

Isfahan Kidney Research Center

By: Hamed Mohamadian Shoeili

Renal Cell Carcinoma

- Renal cell carcinoma (RCC) is commonly encountered in the practice of nephrology, particularly when acute kidney injury (AKI) or chronic kidney disease (CKD) develops in patients with RCC or when a mass is incidentally discovered during workup of kidney disease
- Renal cell carcinoma accounts for approximately 3% of adult malignancies

Renal Cell Carcinoma

- Clear cell RCC, is the most common histological subtype.
- papillary,
- other rare tumors

Clear cell RCC

Von-Hippel Lindau (VHL) disease
Gene: VHL (3p25-26) Protein: VHL protein

Phenotypic features: RCC, hemangioblastoma, pheochromocytoma, renal and pancreatic cysts, ovarian cystadenoma, epididymal cystadenoma

BRCA-associated protein 1 (BAP1) mutations and familial kidney cancer
Gene: BAP1 (3p21) Protein: BRCA-associated protein

Phenotypic features: RCC, breast cancer, mesothelioma, cutaneous melanocytic tumors

Succinate dehydrogenase (SDH)-associated kidney cancer

Gene: SDHB (1p36); SDHC (1q23); SDHD (11q23)

Protein: Succinate dehydrogenase subunits B, C, and D

Phenotypic features: RCC, paragangliomas, pheochromocytoma, carotid body tumor

Papillary RCC

Hereditary papillary RCC (type 1 papillary)
Gene: MET (7q31) Protein: Hepatocyte growth factor receptor

Phenotypic features: None

Hereditary leiomyomatosis and RCC (type 2 papillary)
Gene: FH (1q43) Protein: Fumurate hydratase

Phenotypic features: RCC, uterine leimyosarcomas, breast and bladder cancer, cutaneous and uterine leiomyomas

Other RCC types

Birt-Hogg-Dubé disease
Gene: FLCN (17p11.2) Protein: Folliculin

Phenotypic features: RCC, fibrofolliculomas and trichodiscomas, pulmonary cysts

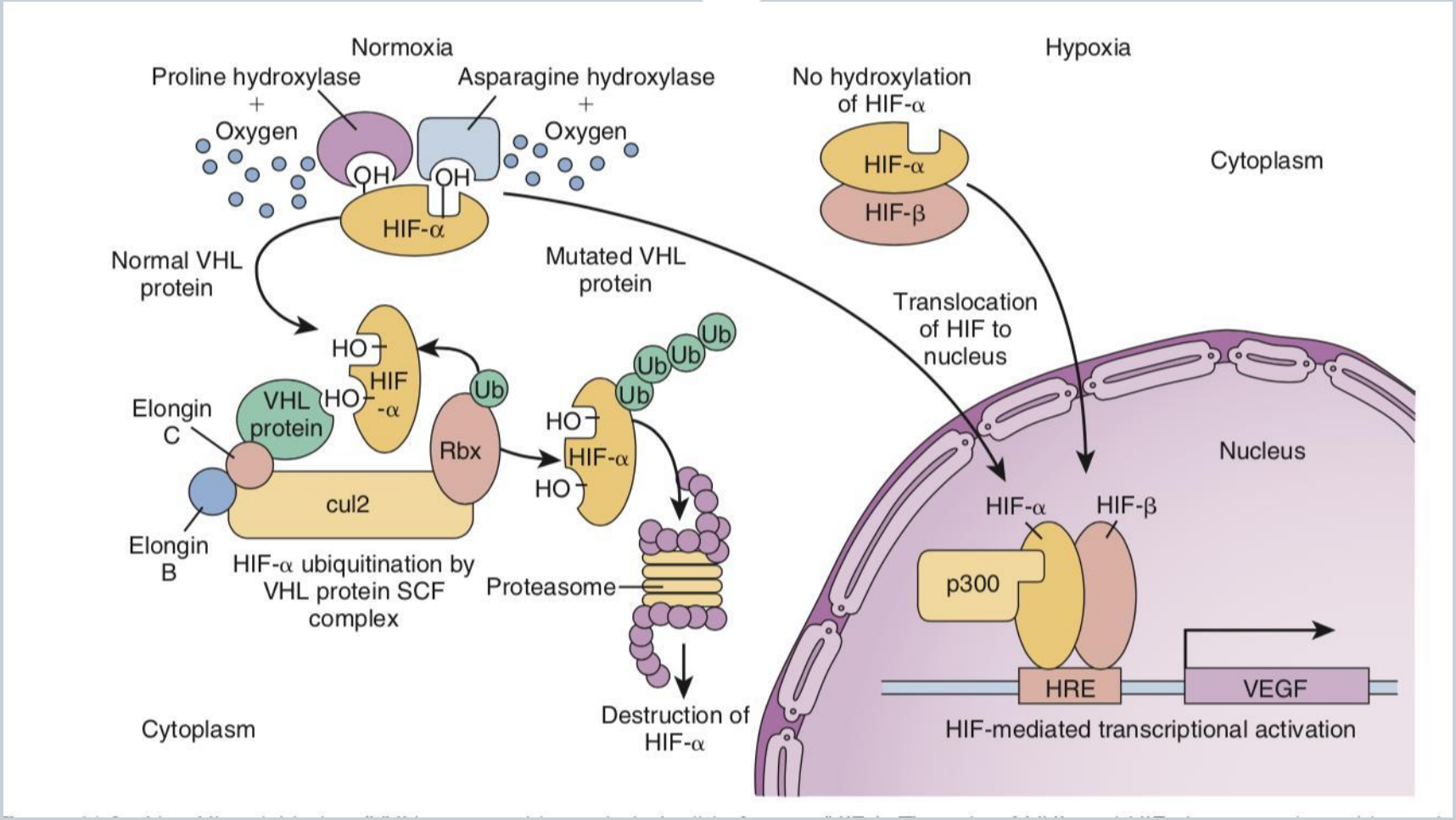
Hamartoma tumor syndrome (Cowden syndrome)
Gene: PTEN (10q23) Protein: Phosphatase and tensin homologue

Phenotypic features: RCC, cancer (breast, endometrial, thyroid, prostate), macrocephaly, benign skin tumors, intestinal hamarotomatous polyps, cerebellar gangliocytoma

Tuberous Sclerosis Complex (TSC)
Gene: TSC1 (9q34); TSC (16p13) Protein: Hamartin and tuberin

Phenotypic features: RCC, angiomyolipoma, renal cysts, subependymal giant cell astrocytomas, facial angiofibromas, ungula and periungual fibromas, hypomelanotic macule, cardiac rhabdomyomas, connective tissue nevus, forehead plaque

Pathogenesis



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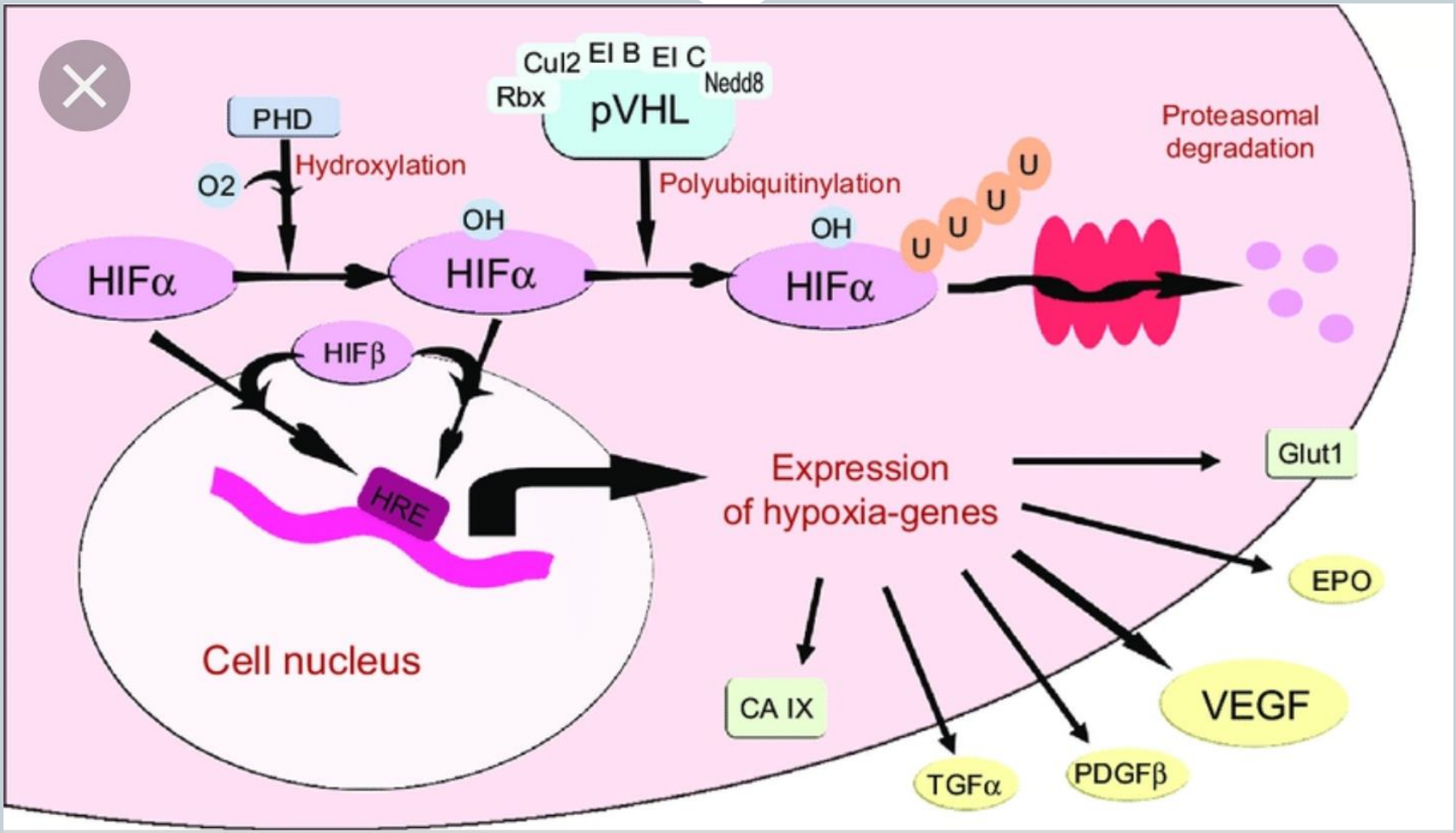
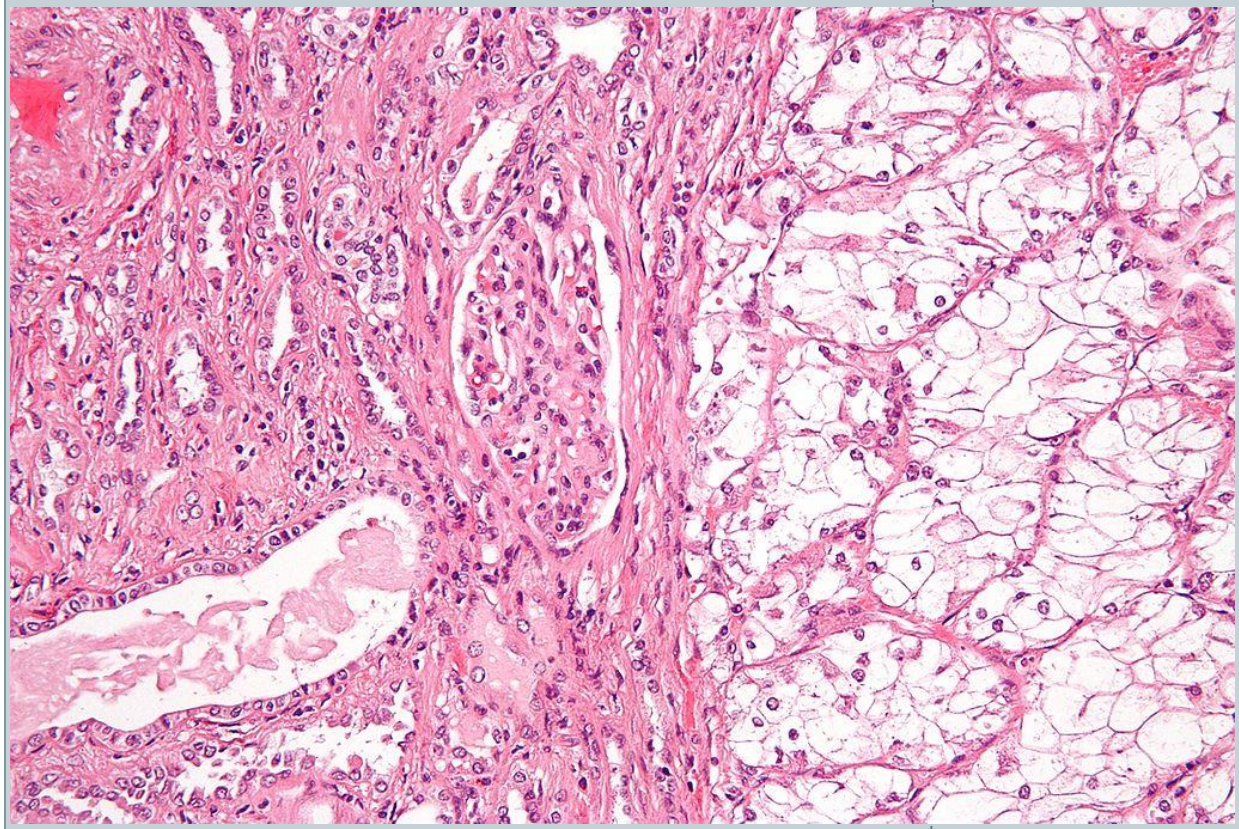
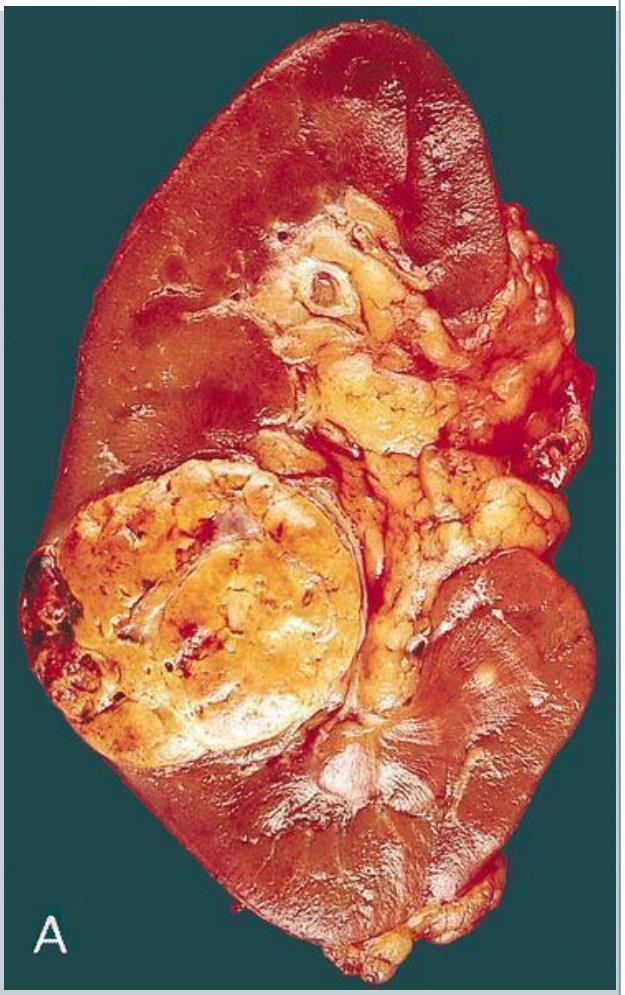


Clear cell RCC





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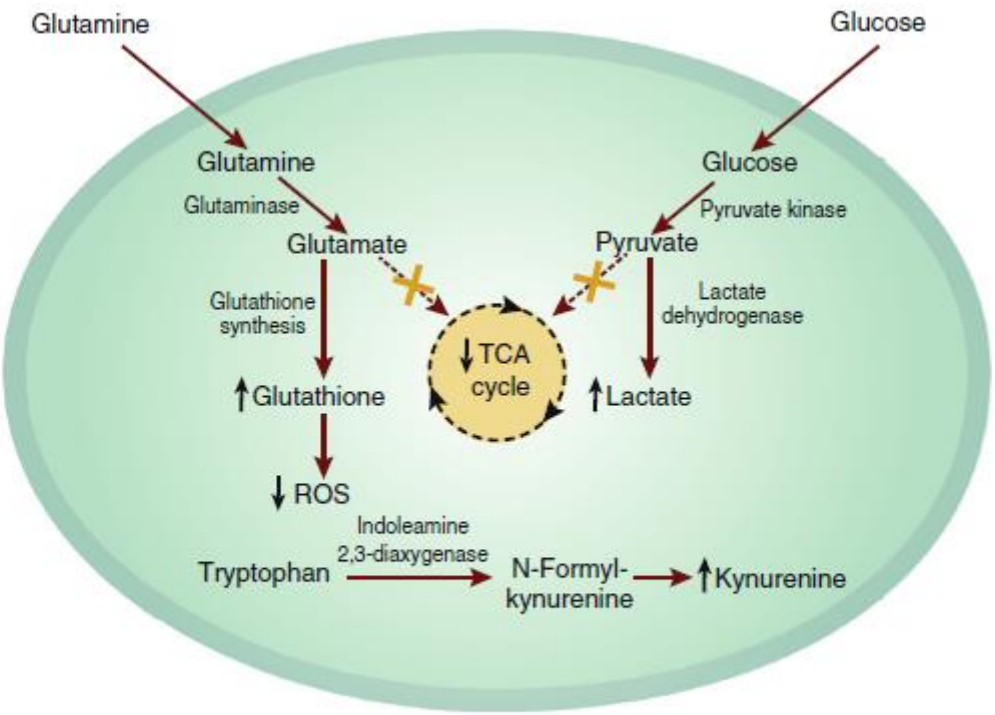

Figure 1 | Dysregulated metabolic pathways in clear cell renal cell carcinoma. Renal cancer cells increase glucose uptake, glycolysis, and lactate production, which results in decreased entry of pyruvate into the tricarboxylic acid (TCA) cycle. Cancer cells also have altered glutamine metabolism, which generates glutathione and reduces reactive oxygen species (ROS). Cancer cells also increase tryptophan metabolism, which causes increased levels of the kynurenine, an immunosuppressive metabolite. These pathways offer targets for renal cell carcinoma treatment.

- Mutations seen in the (PBRM1) gene, which is located on chromosome 3p21 near VHL, is the second major clear cell RCC gene mutation and occurs in approximately 30% to 40% of cases of sporadic RCC.
- A mutation in the BRCA-associated protein-1 (BAP1) gene, which is located at 3p, is also associated with RCC.

Clear cell RCC

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Papillary RCC

Hereditary papillary RCC (type 1 papillary)

Risk Factors

- Tobacco abuse (2- to 3-fold)
- Obesity (1.8 fold in body mass index > 35 kg/m2)
- Hypertension
- Acquired renal cystic disease
- Diabetes mellitus:
  - Excessive insulin levels
  - Obesity-related inflammatory cytokines
  - Insulin resistance

Table 2 | Nongenetic risk factors for renal cell carcinoma

Etiological Risk Factor
Chronic end-stage renal disease on dialysis
Obesity
Smoking
Hypertension
Exposure to dry cleaning solvents
Exposure to trichloroethylene
Diuretics
Radiation therapy
Phenacetin
Arsenic
Cadmium
Sickle cell trait and disease
Nephrolithiasis
Chronic hepatitis C infection

Diagnosis and staging of renal cell carcinoma

- only 10% of patients manifest the classical triad of hematuria, flank pain, and a flank mass
- 25% to 35% of patients have their RCC discovered on imaging performed for an unrelated indication
- Other signs and symptoms :

weight loss, HTN, night sweats, malaise, and the new onset of a varicocele

Para neoplastic phenomena :

- Fever
- Anemia
- Hypercalcemia
- Erythrocytosis
- Elevation of liver enzymes not due to metastatic spread (Stauffer syndrome)
- Rarely Amyloid A amyloidosis
- Polyneuropathy

Diagnosis of renal cell carcinoma

- CT scan with contrast
- MRI
- Sonography
- PET scan
- Biopsy:

- If the tumor is low-grade in nature or if the patient has significant comorbid conditions that increase the risk of a surgical intervention or a limited life expectancy
- Percutaneous kidney mass biopsy has a low complication rate (<5%) and a high diagnostic yield (>90%) with an extremely low risk of seeding malignant cells outside the primary tumor

staging of renal cell carcinoma

Table 3 | Tumor, nodes, metastasis (TNM) staging for renal cell carcinoma

Stage	Definition	Subdivision
Tumor stage		
T0	No evidence of primary tumor	
T1	<7 cm in greatest distance, confined to the kidney	1a: <4 cm 1b: >4 cm and <7 cm
T2	>7 cm in greatest distance, confined to the kidney	2a: >7 cm and <10 cm 2b: >10 cm
T3	Extends into major veins or perinephric tissues but not to adrenal gland or beyond Gerota fascia	3a: Tumor extends into renal vein or invades perirenal sinus fat 3b: Tumor extends into the subdiaphragmatic IVC 3c: Tumor extends into the supradiaphragmatic IVC
T4	Tumor invades beyond Gerota fascia and/or contiguous extension into ipsilateral adrenal gland	
Regional lymph nodes		
N0	No regional lymph node metastasis	
N1	Metastasis to regional lymph nodes	
Distant metastases		
M0	No distant metastasis	
M1	Distant metastasis	

Sites and Frequencies of Metastases

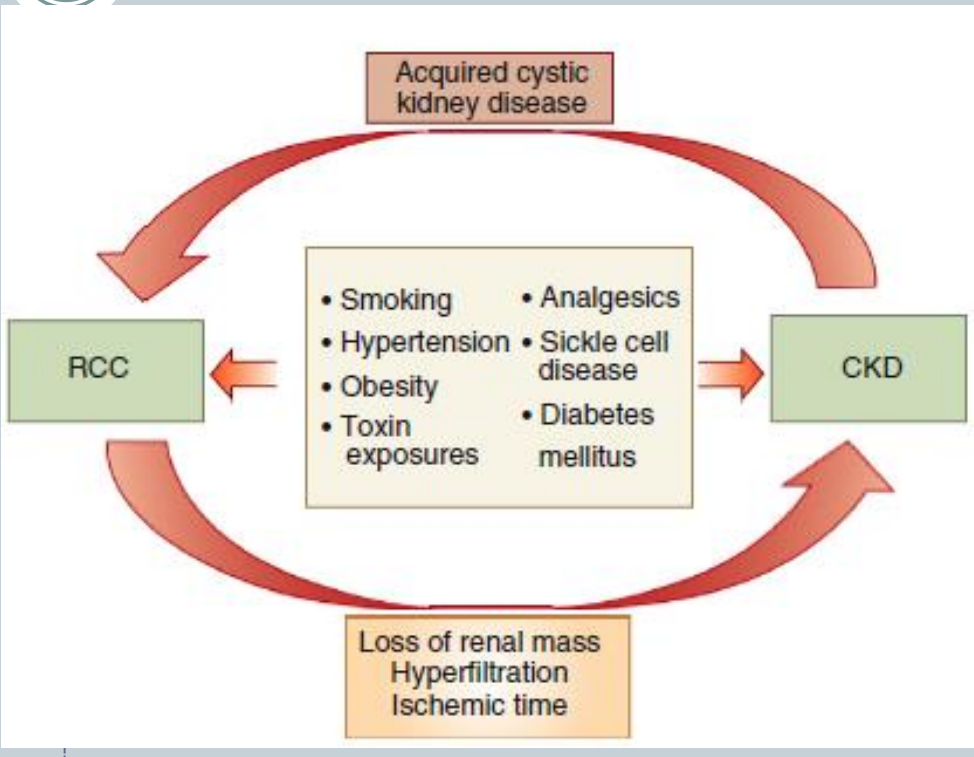
Table 41.3 Sites and Frequencies of Metastases in Renal Cell Carcinoma

Site	Incidence (%)
Lung	50-60
Lymph node	30-40
Bone	30-40
Liver	30-40
Adrenal	20
Opposite kidney	10
Brain	5

From McDougal WS, Garnick M: Clinical signs and symptoms of kidney cancer. In Vogelzang NJ, Scardino PT, Shipley WU, et al (editors): Comprehensive textbook of genitourinary oncology, *Baltimore, 1996, Williams & Wilkins.*

Association of kidney disease with RCC

- 20% to 50% increased risk for all cancers both among patients with early-stage CKD and in those requiring dialysis
- 2- to 3-fold increased cancer risk (all cancers) in kidney transplant recipients
- The cancer risk increased by 29% with every 10 ml/min per 1.73 m2 eGFR decrease, with the greatest risk observed with an eGFR < 40 ml/min per 1.73 m



Association of kidney disease with RCC

- In ESRD patients on dialysis, increased risk for renal parenchymal cancer is related to acquired renal cystic disease, which increases with time on dialysis. Importantly, most of these cancers are papillary rather than clear cell renal cell carcinomas
- CKD with analgesic nephropathy and aristolochic acid nephropathy was also associated with increased incidence of upper urinary tract urothelial carcinomas

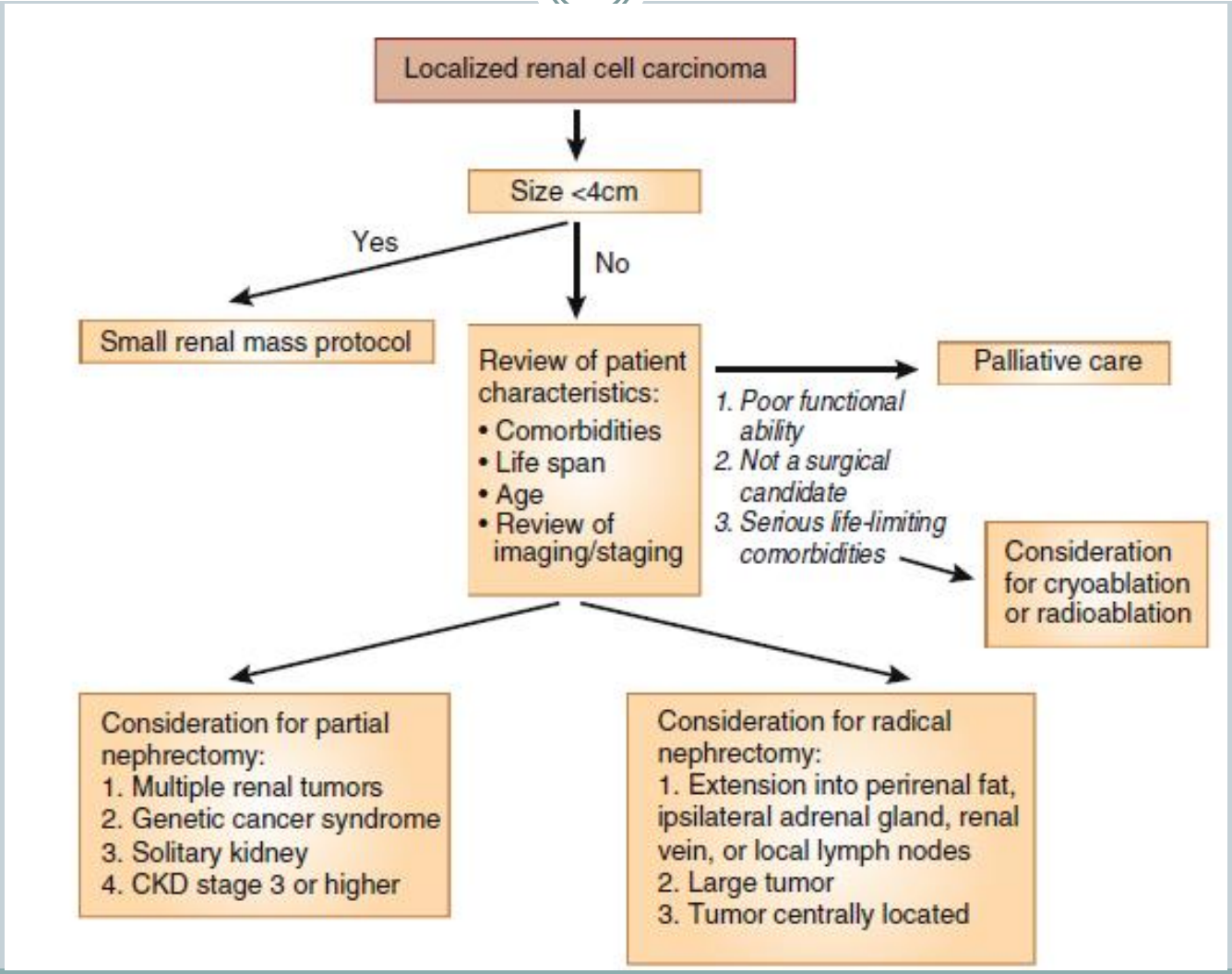
Kidney disease complicating

- Dramatic improvement in 5-year survival for T1 tumors
- CKD is present in approximately 25% of RCC patients prior to receiving any nephrotoxic chemotherapy or undergoing nephrectomy, which significantly increases following surgery

Approach to treatment of RCC

- The decision as to whether to proceed with a radical nephrectomy versus a partial nephrectomy is individualized and guided by the extent of disease, location of the cancer, and patient-specific factors such as comorbidities and age.
- Radical nephrectomy is generally indicated for those patients who have evidence of tumor involvement of the renal vein, adrenal vein, or perinephric fat
- For those patients with a single metastasis and a resectable, localized cancer, surgery focusing on removal of the primary tumor and metastasis (metastasectomy)

Approach to treatment of RCC



Systemic Therapy

- Memorial Sloan Kettering risk criteria (good, intermediate, and poor risk) :
  - Poor performance status
  - High serum calcium
  - High lactase dehydrogenase levels
  - Anemia
  - Short interval from diagnosis to treatment
- Front-line therapy for patients with good or intermediate risk metastatic clear cell renal cancer typically consists of either sunitinib or pazopanib (TKI)

Systemic Therapy

- For much of the past decade, patients whose disease progressed on the initial TKI were subsequently managed with either the oral mTOR inhibitor (everolimus and temsirolimus) or another potent TKI, axitinib.
- Following the recent approvals of both cabozantinib and nivolumab, the management of patients whose disease has progressed on initial TKI has evolved
- The current therapeutic approach of papillary renal cell carcinoma is broadly similar to the management of clear cell renal cancer, albeit with poorer clinical outcomes.

Systemic Therapy

Table 5 | FDA-approved agents for advanced renal cell carcinoma

Drug	Mechanism of action	Nephrotoxicity
High dose Interleukin-2	Cytokine, promotes differentiation of T cells	Prerenal AKI and ischemic ATI/ATN
Temsirolimus	Parenterally administered inhibitor of mTORC1	Increased serum Cr, rare ATI/ATN and glomerulopathy
Everolimus	Oral inhibitor of mTORC1	AKI, proteinuria
Bevacizumab	Recombinant humanized monoclonal antibody inhibitor of VEGF A	Hypertension, proteinuria, TMA, AIN, other GNs
Sorafenib	Small molecule inhibitor of VEGFR, PDGFR and Raf family kinases	Hypertension, proteinuria, AIN, MCD/FSGS, TMA
Sunitinib	Small molecule inhibitor of multiple receptor tyrosine kinases including VEGR and PDGFR	Hypertension, proteinuria, AIN, MCD/FSGS, TMA
Pazopanib	Small molecule multi-targeted tyrosine kinase inhibitor	HTN, proteinuria
Axitinib	Small molecule inhibitor of VEGFR 1-3, c-KIT and PDGFR	HTN, proteinuria
Lenvatinib	Small molecule multi-targeted tyrosine kinase inhibitor	Rare proteinuria, increased serum Cr
Cabozantinib	Small molecule inhibitor of c-Met, VEGFR2, AXL	HTN, rare proteinuria and increased serum Cr
Nivolumab	Anti PD-1 antibody	AIN (+/- granulomatous), MCD, IC-GN

AIN, acute interstitial nephritis; ATI/ATN, acute tubular injury/necrosis; Cr, creatinine; FSGS, focal segmental glomerulosclerosis; HTN, hypertension; MCD, minimal change disease; mTORC1, mammalian target of rapamycin complex 1; PD1, programmed cell death 1 ligand; PDGFR, platelet-derived growth factor receptors; TMA, thrombotic microangiopathy; VEGFR, vascular endothelial growth factor receptor.

از توجه شما سپاسگزارم