Renal Masses

Dr. Jad AlSmadi, MD.,

Lecturer with Assistant Professor duties,

faculty of medicine,

The Hashemite University

General: Renal Mass

- When symptoms are present, common symptoms are flank pain, a palpable mass, and hematuria.
- However, most diagnoses result from an incidental renal mass.
- Indicators of benign mass: 1. thin, unenhanced walls in simple cyst disease. 2. macroscopic fat in an AML. 3. smaller mass size. 4. lack of growth in serial imaging. 5. female sex.
- However, none except for lack of growth over time, can ***reliably rule out*** malignancy.

Benign: Renal Cyst

- The most common benign entity encountered in the kidney.
- Up to 10% of the population may harbor a renal cyst
- Risk factors: increasing age, male gender, hypertension, and worsening renal function
- Renal cysts can be sporadic, acquired, or genetic in their origin
- Presentations: Mostly incidental, can cause pain from local expansion, a palpable mass, hematuria, and, in the case of ADPKD, pulmonary symptoms from mass effect.

Benign: Renal Cyst

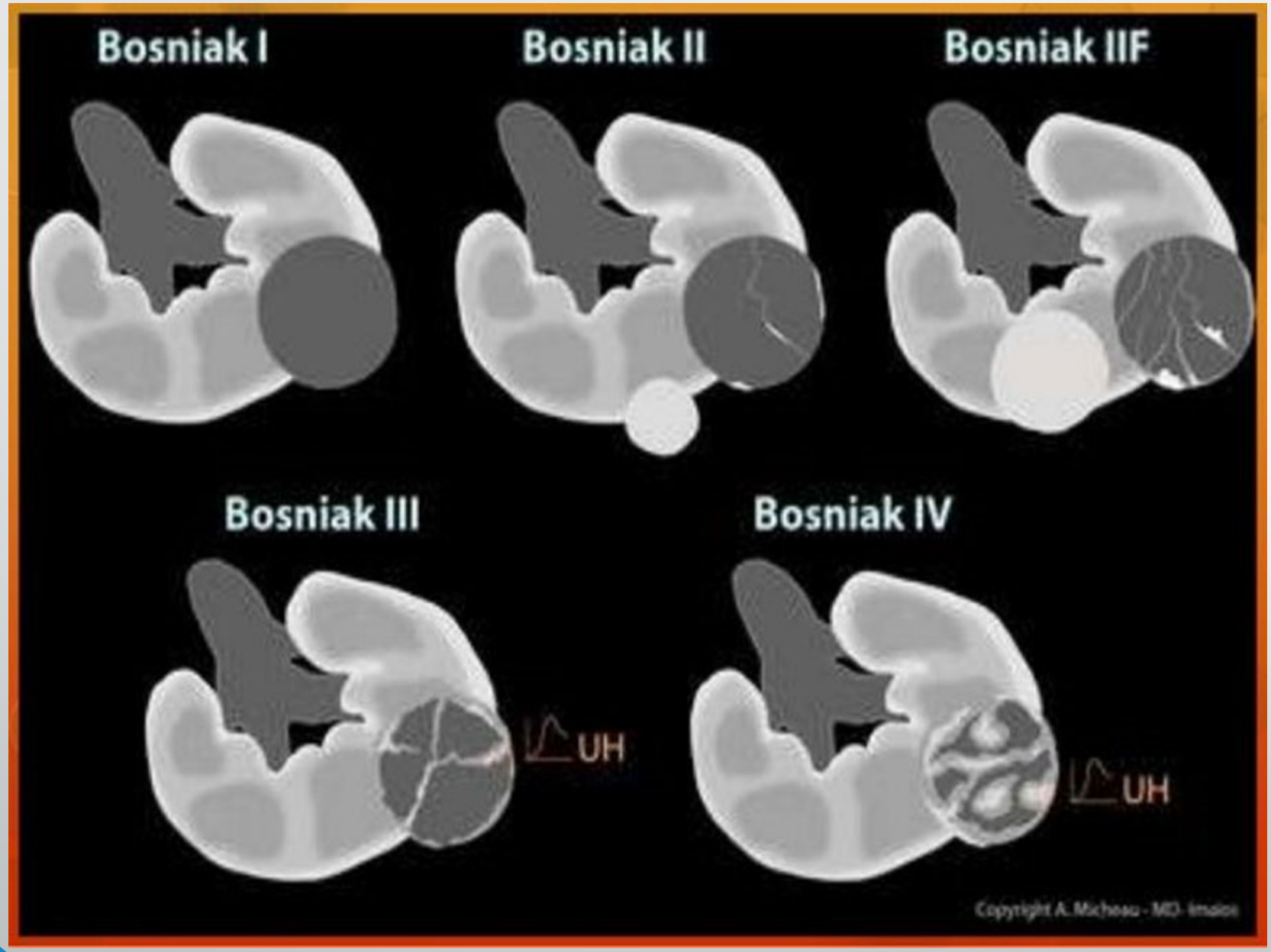
- Evaluation➔ imaging: include US, CT, or MRI.
- The goal of imaging in cystic renal disease is evaluation of malignancy risk as defined by increasing complexity
- **Simple renal cysts** are: smooth walls, sharp outlines, and the absence of internal echoes on ultrasonography
- To aid in the evaluation of renal cyst disease, the **Bosniak classification** is a commonly used method to characterize cysts and their risk of malignancy.

Classification of Complex Renal Cysts

BOSNIAK CLASSIFICATION	RADIOGRAPHIC FEATURES	RISK OF MALIGNANCY	MANAGEMENT
I	Water density, Homogeneous, hairline thin wall No septa, No calcifications, No enhancement	None	Surveillance not necessary
II	Few hairline septa In which "perceived" enhancement may be present Fine calcification or short segment of slightly thickened calcification in wall or septa No unequivocal enhancement	Minimal	Surveillance not necessary
	Hyperdense lesion: ≤3 cm, well marginated, with no unequivocal enhancement	Minimal	Periodic surveillance

Classification of Complex Renal Cysts

BOSNIAK CLASSIFICATION	RADIOGRAPHIC FEATURES	RISK OF MALIGNANCY	MANAGEMENT
IIF	Multiple hairline thin septa, Minimal smooth wall thickening "Perceived" enhancement of wall or septae may be present Calcification may be thick or nodular but must be without enhancement Generally well marginated No unequivocal enhancement	3%–5%	Periodic Surveillance
	Hyperdense lesion: >3 cm or totally intrarenal with no enhancement	5%–10%	Periodic surveillance
III	"Indeterminate," thickened irregular or smooth walls or septa in which **measurable enhancement** is present	50%	Surgical Excision
IV	Clearly malignant lesions that can have all the criteria of category III but also contain enhancing soft-tissue components	75%–90%	Surgical excision


Bosniak I
Bosniak II
Bosniak IIF
Bosniak III
UH
Bosniak IV
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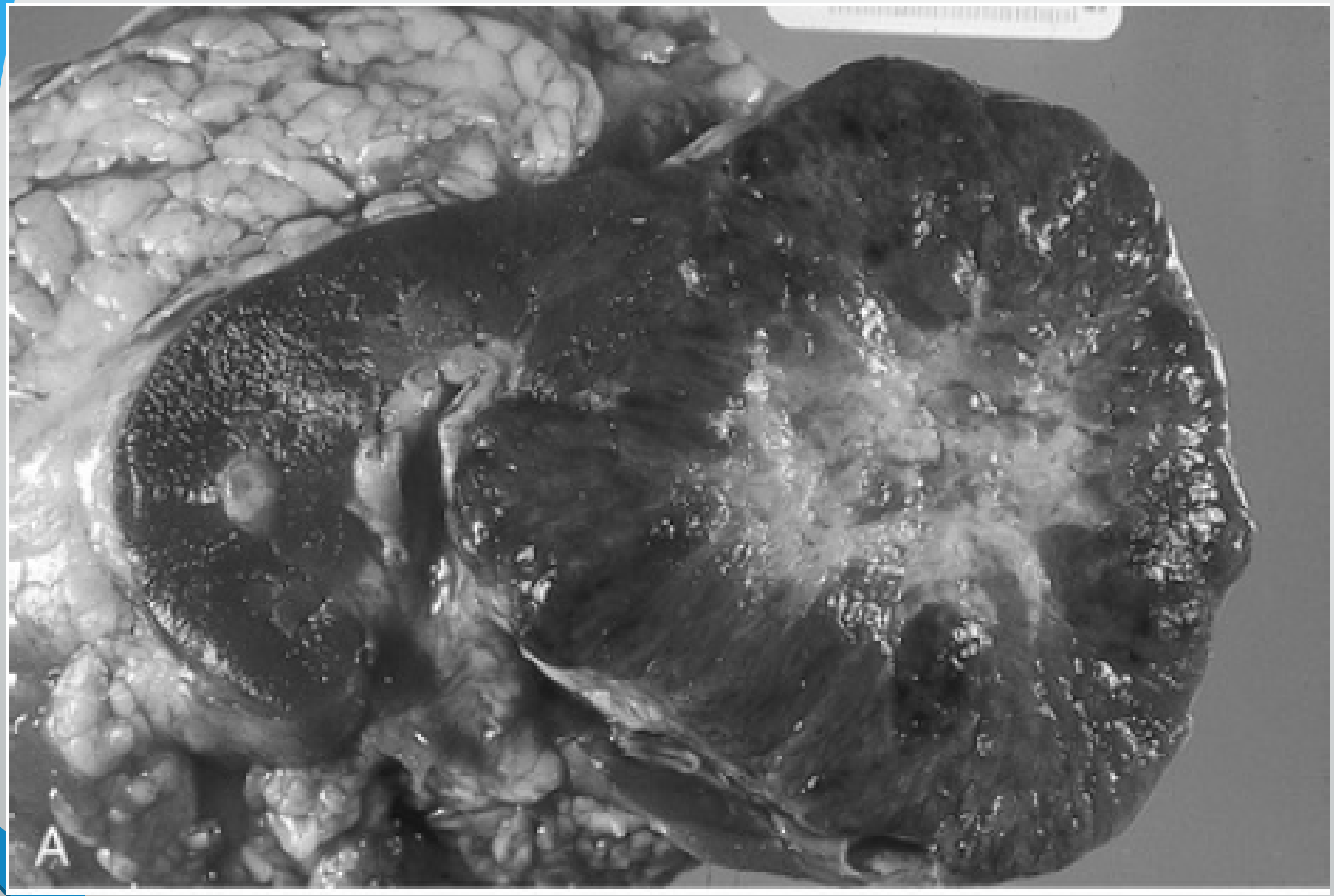
Benign: Renal Cyst management

- The management of renal cyst disease is based on the risk of malignancy and the associated symptoms
- Most Simple Renal cysts do not require further management
- Indications for treatment: local symptoms such as pain, infection, hypertension, hemorrhage, or traumatic cyst rupture.
- Management can include: **aspiration**, **cyst decortication**, **cyst resection**, **sclerotherapy**, **arterial embolization**, and even **nephrectomy** depending on the cause and symptom

Benign: Oncocytoma

- **The most common benign enhancing** renal mass
- 25% of renal masses smaller than 3 cm represent oncocytomas
- Pathologically, have overlapping features with eosinophilic chromophobe RCC, succinate dehydrogenase-deficient RCC, and papillary RCC.
- Grossly, these tumors have a mahogany brown surface, similar to the appearance of normal renal parenchyma, with a variably present central scar.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Benign: Oncocytoma

- Histologically, these tumors are classically strongly eosinophilic because of the high ***mitochondrial* density**, with nests and tubular structures common, arising from the distal tubule.
- Nuclei tend to be round and regular with extremely rare mitotic figures
- Oncocytoma can be associated with perirenal fat invasion and renal vein invasion—findings that carry prognostic significance in RCC but do not in oncocytoma and **should not be interpreted as an aggressive pathology.**

Benign: Oncocytoma Evaluation

- Definitive diagnosis of oncocytoma is typically postoperative.
- Hypervascularity and a central scar on axial imaging can suggest oncocytoma as the diagnosis.
- When suspicion of oncocytoma is high based on imaging, renal mass biopsy has been used with some success. However, positive predictive value for oncocytoma is low.
- The mainstay management is postsurgical observation.

Benign: Angiomyolipoma (AML)

- A benign renal entity composed of dysmorphic blood vessels, smooth muscle, and adipose tissue
- can occur sporadically or as part of genetic syndromes: most commonly tuberous sclerosis complex (TSC) and lymphangioleiomyomatosis (LAM).
- The prevalence at 0.13% in the general population, with a female predisposition and a peak in the fourth and fifth decade.
- Among TSC patients, the prevalence has been reported from 55% to 90%, with an earlier presentation than sporadic cases.

Benign: Angiomyolipoma (AML)

- Diagnosis: Mostly incidental, or
- **Wunderlich syndrome**: spontaneous retroperitoneal hemorrhage
- The diagnosis of AML can be made on imaging: presence of macroscopic fat on CT or MRI **is diagnostic** of AML.
- Management of patients with an AML should be individualized on the basis of sporadic versus syndromic AML, the presence of symptoms, and the perceived risk of hemorrhage.
- Active Surveillance: less than 4 cm in size are expected to be asymptomatic and unlikely to bleed.

Benign: Angiomyolipoma (AML)

- Size of 4 cm or greater and being of child-bearing age were used as indications for intervention.
- There are four mainstays of therapy: surgical resection, thermal ablation, embolization, and systemic therapy with mTOR inhibitors.

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- When resection is chosen, nephron-sparing approaches should be performed (e.g. **Partial Nephrectomy**).
- **Selective arterial embolization**: for the management of acute hemorrhage in AML, in which operative intervention most often results in total nephrectomy.

Benign: Papillary Adenoma

- Is a low-grade (grade 1–2), well-circumscribed cortical lesion measuring less than 0.5 cm.
- Incidence increases with age, male sex, end-stage renal disease, acquired renal cystic disease, sporadic RCC, and hereditary papillary RCC.
- Papillary adenomas are associated with papillary RCC (47%)
- Are often diagnosed pathologically as a concomitant finding with RCC and therefore require no further directed therapy.

Malignant: RCC

- Renal masses are a biologically heterogeneous group of tumors ranging from benign masses to cancers that can be indolent or aggressive
- Peak Incidence bet. 55-75 with M:F = 1.9:1.
- RCC, which accounts for 2% to 3% of all adult malignant neoplasms, is the most lethal of the common urologic cancers.
- The majority of cases of RCC are sporadic; only 4% to 6% are believed to be familial.

RCC: Etiology

1. Smoking: well-established risk factor, the associated relative risks have been modest, ranging from 1.4 to 2.5 compared with controls.

- Tobacco use accounts for 20% to 30% of cases of RCC in men and 10% to 20% in women

2. Obesity: increased relative risk of 1.07 for each additional unit of body mass index

➔ obesity paradox: Higher risk for low-grade, early stage tumors.

RCC: Etiology

3. Hypertension: the third major causative factor for RCC.

- The proposed mechanisms are hypertension-induced renal injury and inflammation or metabolic or functional changes in the renal tubules that may increase susceptibility to carcinogens.
- Pathology: Most RCCs are round to ovoid and circumscribed by a pseudocapsule of compressed parenchyma and fibrous tissue.
- with the exception of oncocytomas and some small (≤5 mm) low grade papillary adenomas, there are no reliable histologic or ultrastructural criteria to differentiate benign from malignant renal epithelial tumors

Modified 2016 World Health Organization classification of renal neoplasms with focus on adult neoplasms

Renal cell tumors	Benign renal tumors
Clear cell RCC	Papillary adenoma
Multilocular cystic renal neoplasm of low malignant potential	Oncocytoma
Papillary RCC	Angiomyolipoma
Hereditary leiomyomatosis RCC	Metanephric adenoma and other metanephric tumors
Chromophobe RCC	Adult cystic nephroma
Collecting duct carcinoma	Mixed epithelial stromal tumors
Renal medullary carcinoma	Juxtaglomerular cell tumor
MiT Family translocation carcinomas	
Succinate dehydrogenase (SDH) deficient RCC	**Mesenchymal tumors**
Mucinous tubular and spindle cell carcinoma	Leiomyosarcoma (including renal vein) and other sarcomas
Tubulocystic RCC	Leiomyoma and other benign mesenchymal tumors
Acquired cystic disease associated RCC	
Clear cell papillary RCC	
RCC, unclassified	

RCC: Grading

- Grading has been based primarily on nuclear size and shape and the presence or absence of prominent nucleoli.

World Health Organization/International Society of Urological Pathology (WHO/ISUP) Grading System for Clear Cell and Papillary Renal Cell Carcinoma

GRADE	DESCRIPTION
1	Nucleoli are absent or inconspicuous and basophilic at 400× magnification
2	Nucleoli are conspicuous and eosinophilic at 400× magnification and visible but not prominent at 100× magnification
3	Nucleoli are conspicuous and eosinophilic at 100× magnification
4	There is extreme nuclear pleomorphism, multinucleated giant cells, and/or rhabdoid and/or sarcomatoid differentiation

RCC: Pathology

- All RCCs are, by definition, adenocarcinomas, derived from renal tubular epithelial cells.
- Most RCCs share ultrastructural features, such as surface microvilli and complex intracellular junctions, with normal proximal tubular cells and are believed to be derived from this region of the nephron
- Chromophobe RCC, renal medullary carcinoma and collecting duct carcinoma, appear to be derived from more distal elements of the nephron

Clear Cell Renal Cell Carcinoma

- The most common subtype accounting for 70% to 80% of all RCCs, typically yellow and highly vascular.
- Clear cells are typically round or polygonal with abundant cytoplasm containing glycogen, cholesterol, cholesterol esters, and phospholipids.
- clear cell RCC have a worse prognosis compared with **papillary type 1** or **chromophobe RCC**.
- Paradoxically, clear cell RCC is more likely to respond to VEGF-targeted therapy, checkpoint inhibitors, or high dose IL-2 than other subtypes of RCC, so it typically has a better prognosis when it is **metastatic**.

Papillary Renal Cell Carcinoma

- Was previously designated chromophilic RCC, is the second most common histologic subtype (10%–15%).
- Gross features of papillary RCC include beige to white color, spherical boundary, and frequent hemorrhage, which may mimic cystic components radiologically.
- One **unique feature** of papillary RCC is its tendency toward multicentricity, which approaches 40%.
- occurs more commonly in patients with end-stage renal disease and acquired renal cystic disease.

Papillary Renal Cell Carcinoma

- **Type 1 papillary RCC**, the more common form, consists of basophilic cells with scant cytoplasm;
- **Type 2 papillary RCC** includes potentially more aggressive variants with eosinophilic cells and abundant granular cytoplasm
- **Type 1 papillary RCC** carries a better prognosis than clear cell RCC, whereas **type 2 papillary RCC** is similar or worse than clear cell RCC.

Chromophobe Renal Cell Carcinoma

- Represents 3% to 5% of all RCCs and appears to be derived from the distal convoluted tubules.
- Commonly seen in the BHD syndrome, but most cases are sporadic.
- Localized chromophobe RCC has better prognosis than for clear cell RCC.
- But a poor outcome in patients with sarcomatoid features or metastatic disease.
- Has the tendency of growing to large sizes thus presenting at an earlier T stage.

Collecting Duct Carcinoma

- Carcinoma of the collecting ducts of Bellini is a relatively rare subtype of RCC, with a predictably poor prognosis.
- Small collecting duct carcinomas can arise in a medullary pyramid, but most are large, infiltrative masses, and extension into the cortex is common.
- On microscopic examination, these tumors consist of an admixture of dilated tubules and papillary structures typically lined by a single layer of cuboidal cells, often creating a cobblestone appearance.
- Usually has high grade, advanced stage, and unresponsive to conventional therapies

Clinical Presentations

- Because of the sequestered location of the kidney within the retroperitoneum, many renal masses remain asymptomatic and nonpalpable until they are locally advanced
- More than 60% of RCCs are now detected incidentally.
- Symptoms associated with RCC can be due to local tumor growth, hemorrhage, paraneoplastic syndromes, or metastatic disease.
- The classic triad of flank pain, gross hematuria, and palpable abdominal mass is now rarely seen

Clinical Presentations

- Flank pain is usually due to hemorrhage and clot obstruction, it also occur with locally advanced or invasive disease.
- Others: Hematuria, Abdominal mass, Perinephric hematoma
- Obstruction of the inferior vena cava: Bilateral lower extremity edema or right-sided varicocele.
- Paraneoplastic syndromes are found in 10% to 20% of patients with RCC.
- Paraneoplastic syndromes are more common in metastatic disease and less common (almost nonexistent) in patients with small, incidental renal masses

Paraneoplastic syndromes

1.The most common of these syndromes **is elevated erythrocyte sedimentation rate**, which accounts for more than 50%.

2. Pathologically producing 1,25-dihydroxycholecalciferol, renin, erythropoietin, prostaglandins, parathyroid hormone–like peptides, lupus-type anticoagulant, human chorionic gonadotropin, insulin, and various cytokines and inflammatory mediators.

3. **Hypercalcemia**: in up to 13% of patients with RCC and can be due to either paraneoplastic phenomena or osteolytic metastatic involvement of the bone.

Paraneoplastic syndromes

4. **Hypertension**: can be due to increased production of renin directly by the tumor; compression or encasement of the renal artery or its branches, effectively leading to renal artery stenosis; or arteriovenous fistula within the tumor.

5. **Polycythemia:** due to increased production of erythropoietin, either directly by the tumor or by the adjacent parenchyma in response to hypoxia induced by tumor growth.

6. **Nonmetastatic hepatic dysfunction**, or ***Stauffer syndrome***, which has been reported in 3% to 20% of cases.

7. Others: Cushing syndrome, hyperglycemia, galactorrhea, neuromyopathy, clotting disorders, and cerebellar ataxia

International TNM Staging System

T: PRIMARY TUMOR	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1a	Tumor ≤ 4.0 cm and confined to the kidney
T1b	Tumor > 4.0 cm and ≤7.0 cm and confined to the kidney
T2a	Tumor > 7.0 cm and ≤10.0 cm and confined to the kidney
T2b	Tumor > 10.0 cm and confined to the kidney
T3a	Tumor extends into the renal vein or its segmental branches, or invades the pelvicalyceal system, or invades perirenal and/or renal sinus fat but not beyond Gerota fascia
T3b	Tumor grossly extends into the vena cava below the diaphragm
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)

International TNM Staging System

NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph nodes metastasis		
N1	Metastasis in regional lymph node(s)		
M: DISTANT METASTASES			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis present		
STAGE GROUPING			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1 or T2	N1	M0
	T3	Any N	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

Treatment of Localized RCC

- Multiple management strategies are available, including RN (Radical Nephrectomy), PN (Partial Nephrectomy), thermal ablation (TA), and active surveillance (AS).
- **1. Active Surveillance (AS)**: for patients with clinically localized small renal masses (cT1a, ≤4cm)
- Patients are evaluated every 3-6 months for two years and with extended imaging intervals beyond that

Treatment Alternatives/ localized

2. Radical Nephrectomy (RN):

- Was the mainstay of therapy for all renal masses for many decades. Prototypically, RN included the removal of the entire kidney including Gerota's fascia, regional lymph nodes and the adrenal gland.
- RN can be performed through an open incision or via minimally-invasive approaches (laparoscopic or robotic).
- Cancer-specific survival associated with RN is excellent however recent controversies regarding RN include its negative impact on renal function and overutilization for the management of stage I, especially T1a, tumors.

Treatment Alternatives/ localized

2. Radical Nephrectomy (RN):

- NOW: Removal of the ipsilateral adrenal gland is not routinely necessary.
- Indications to remove the adrenal: radiographic adrenal enlargement or local invasion, the malignant lesion is extensively involving the kidney and/or is locally advanced.
- Extensive LND is not done in all patients: because RCC metastasizes through the bloodstream independent of the lymphatics in many patients, and the lymphatic drainage of the kidney is highly variable.

Treatment Alternatives/ localized

2. Radical Nephrectomy (RN):

- Indications for LND during RP: when suspicious lymphadenopathy is identified on imaging or surgical exploration; can be selectively considered for locally advanced disease.
- And in all of these settings LND is primarily for staging and prognostic purposes
- Laparoscopic RN is **the standard of care**: less-morbid in low- to moderate-volume RCCs with no local invasion, limited or no venous involvement, and manageable lymphadenopathy.

Treatment Alternatives/ localized

3. Partial Nephrectomy (PN):

- Entails complete local resection of the tumor while optimally preserving normal functioning parenchyma within the involved kidney.
- Either through an open incision or via a minimally invasive.
- PN carries increased risk of urologic complications, although most are manageable and typically associated with good outcomes.
- **Indications for PN**: in situations in which RN would render the patient anephric or at high risk for ultimate need of dialysis.

Treatment Alternatives/ localized

3. Partial Nephrectomy (PN):

- **Indications for PN**: bilateral synchronous RCC, RCC involving a functionally or anatomically solitary kidney.
- **PN is now standard of care for the management of small renal masses (clinical T1a) in the presence of a normal contralateral kidney.**
- **PN for T1a RCC demonstrated local recurrence rates of 1% to 2%, and overall cancer-free survival well over 90%.**

Treatment Alternatives/ localized

4. Thermal Ablation (TA): were developed to improve patient procedural tolerance and reduce the potential for complications from PN, while still preserving function.

- including renal cryosurgery and radiofrequency ablation (RFA).
- Both can be done percutaneously and offer reduced morbidity
- disadvantages: lack of pre and post treatment biopsy to define malignancy and efficacy, and increased local recurrence rates relative to surgical excision.

Treatment: locally advanced RCC

- In the presence of clinically positive LNs (cN+), LND is always justified.
- Tumor thrombus in the setting of non-metastatic disease should be excised (IVC thrombectomy).
- Tumor embolization or IVC filter do not appear to offer any benefits in the treatment of tumor thrombus.
- For locally advanced and invasive (stage T_4) RCC surgical therapy is the only potentially curative management for with en-bloc resection of adjacent organs are occasionally indicated

Treatment: advanced/metastatic RCC

Cytoreductive nephrectomy (CN):

- Tumor nephrectomy is curative only if all tumor deposits are excised.
- This includes patients with the primary tumor in place and single- or oligo-metastatic resectable disease
- For most patients with metastatic disease, cytoreductive nephrectomy (CN) is palliative and systemic treatments are necessary

Treatment: advanced/metastatic RCC

Cytoreductive nephrectomy (CN):

- As a palliative option in patients with: intractable pain, hematuria, constitutional symptoms, or a variety of paraneoplastic manifestations such as hypercalcemia, erythrocytosis, secondary thrombocytosis, or hypertension.
- CN is indicated in patients with: good performance who do not require systemic therapy, patients with oligo-metastases, intermediate risk patients under VEGFR-TKI therapy.

Treatment of advanced/metastatic RCC: Local therapy of metastases

- Metastasectomy remains by default the only local treatment for most sites, with exception of brain and possibly bone metastases
- **resection of limited metastatic disease has been reported to be associated with long disease-free intervals and OS.**
- Radiotherapy to bone and brain metastases from RCC can induce significant relief from local symptoms

Targeted therapy: Immunotherapy

- 1) Immune checkpoint inhibition of programmed death receptor (PD-1) and ligand (PD-L1) inhibition: (e.g. nivolumab, ipilimumab, pembrolizumab).
- the combination of pembrolizumab and axitinib showed survival advantage for patients in all risk groups.
- 2) VEGF-tyrosine kinase inhibitors (TkIs): axitinib, Sunitinib
- Offer VEGF-tyrosine kinase inhibitors as second-line therapy
- 3) mTOR inhibitors: drugs that inhibit the mechanistic target of rapamycin: Everolimus, Temsirolimus.

Thank You