Renal Neoplasms

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1. Benign Renal Masses

Introduction

Contemporary surgical extirpation series demonstrate that 15-20% of renal masses smaller than 7 cm in size are comprised of benign histologies[1].The World Health Organization (WHO) has classified benign renal masses based upon cell type of origin and histopathology (**Table 1**).[2,3] A brief discussion of some of the salient histologic subtypes is highlighted below.

1.1 Epithelial Tumors

- Renal oncocytic neoplasms are a broad category of eosinophilic tumors which contain a spectrum of tumors ranging from benign oncocytoma to chromophobe RCC. Entities such as hybrid oncocytic/chromophobe (HOCT), low grade oncocytic tumor, and eosinophilic vacuolated Tumor (EVT) have been recently described.[4,5]
  - **Oncocytomas** account for approximately **15% of adult primary epithelial neoplasms with a roughly 2:1 male to female ratio.**[6]
  - Oncocytomas may occur as part of the Birt-Hogg Dube syndrome.
  - Originate from intercalating cells in the cortical **collecting duct**.
  - Grossly, the lesion is **well-circumscribed, non-encapsulated, mahogany brown with a central stellate scar.**
  - Microscopically, oncocytic cells are often nested with a densely granular eosinophilic cytoplasm with round, regular, homogenous nuclei.
  - Permissible “atypical features” include perirenal fat involvement, hemorrhage, microscopic necrosis, and microvascular invasion. Evidence of gross renal vein involvement, necrosis, frequent mitoses, or extensive papillary architecture are exclusions[7].
  - **Oncocytomas exhibit fewer chromosomal abnormalities than chromophobe RCC. Mutations in chromosomes 1 and 14** as well as **alterations in mitochondrial DNA are frequently observed**.
  - Definitive diagnosis of an oncocytoma on core needle biopsy may be challenging due to intratumoral heterogeneity, and a more general categorical definition of "oncocytic renal neoplasm" may be utilized[8].
  - Contemporary imaging techniques using sestamibi SPECT/CT may aid in distinguishing oncocytic tumors from other renal neoplasms but need further study and validation[9].
  - Recent studies have shown that active surveillance is safe for biopsy-proven oncocytomas[10]
- Papillary Adenoma[11]
  - Solitary, unencapsulated lesion measuring <15mm[11]
  - Typically have loss of Y chromosome and combined trisomy of chromosome 7 and 17
  - Morphologically similar to papillary RCC, but without capacity to metastasize
  - More common in chronic kidney disease

1.2 Mesenchymal Tumors

- Mesenchymal tumors are defined as neoplasms with vascular, fibrous, adipose, or other mesenchymal tissue differentiation.
- **Perivascular epitheliod cell neoplasms (PEComas)** are mesenchymal tumors that form around small blood vessels. Most are benign, but some have malignant potential.
- **Angiomyolipomas (AML)**[12] are the most common PEComa
  - Composed of **variable amounts of blood vessels, smooth muscle, and fat.**
  - Two major histologic variants have been described: Classic (triphasic) and epithelioid (monophasic).

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- Typically stain positive for HMB-45 and melan-A
- Epithelioid AMLs lack macroscopic fat and are radiographically indistinguishable from other solid renal masses
  - Histologically they are a pure or predominant population of polygonal cells with clear or densely packed eosinophilic cytoplasm. Hemorrhage and necrosis are common[13]
  - These tumors have an increased malignant potential (reported as high as 1/3)[14] and patients with malignant features should be followed closely for recurrence.[15]
- Classic AMLs can occur either **sporadically** (70-80%)[16] or in association with the **tuberous sclerosis complex (TSC) or lymphangioleiomyomatosis (LAM).**
- **AMLs associated with TSC grow faster and have a higher rate of malignant transformation.**
- Sporadically occurring AMLs have a 4:1 female to male preponderance
- 80% of all patients with TSC will develop renal AMLs. **Consider a referral for genetic testing in patients with synchronou bilateral AMLs.**[17]
- **Traditionally, size greater than 4 cm and presence of intralesional vascular aneurysms > 5 mm have been associated with AML hemorrhage.**[18] However, studies have also suggested that surveillance may be an acceptable approach in selected larger classic AML.[19,20]
- **More than 90% of AMLs demonstrate very little to no growth on surveillance, regardless of size and** only 9% exceed 0.25cm/year of growth.[21,22] The risk of spontaneous rupture is also low, reported at 2.2% in a recent systematic review.
- **Selective arterial embolization is a commonly used treatment modality, but is associated with a retreatment rate of 30%.**[21]
- Estrogen-receptor-beta is ubiquitously expressed in AMLs (100%) along with androgen receptor (82%), while Estrogen-receptor-alpha and progesterone receptor is expressed in approximately one-third of tumors,[23] which may explain th observation of increased AML growth and risk of hemorrhage in pregnancy or with exogenous hormonal therapy.[24,25,26]
- **Identification of intra-tumoral macroscopic fat on computed tomography (CT) is sufficient to confirm an AML**. Intra-tumoral fat is identified by a mean region of interest (ROI) value of ≤ -10 units.
- Everolimus may be used to treat AML in selected TSC patients. In a placebo-controlled randomized clinical trial, **treatment with everolimus was associated with at least 50% decrease in AML volume for 42% of patients**. The most common adverse events associated with treatment included: stomatitis, naso-pharyngitis and acne-like skin lesions. A total of 73.2% o patients had durable control with everolimus, but AML may resume growth following treatment cessation.[27,28,29]

- **Juxtaglomerular Cell Neoplasm** (reninoma) neoplasms are extremely rare benign mesenchymal tumors.
  - Present in adults during the 2nd and 3rd decades of life.
  - **Classically present with hypertension, hypokalemia, and high serum renin levels.**[30]
  - Will appear hypovascular on contrast enhanced imaging, despite being hypervascular tumors, possibly due to renin induced vasoconstriction
  - Reninomas typically present as solitary, well-circumscribed cortical tumors less than 3 cm in diameter. Microscopy reveals sheets of hemangiopericytic cells. Rhomboid renin protogranules is diagnostic.

1.3 Mixed Epithelial and Stromal Tumor Family

- **Introduced by WHO 2016 as new entity, encompassing tumors composed of an epithelial component that lines a variable cystic architecture and spindle-cell stromal component.**[11] **Tumors range from predominantly cystic (adult cystic nephroma to variably solid (MEST)**
- **Much more common in women (7:1), typically 5th decade**
- **Often express Estrogen and progesterone receptors**
- **Cystic nephroma** typically affects **middle-aged, perimenopausal women** and adult cases are morphologically distinct from pediatric counterparts.
  - Grossly, cystic nephromas are composed of non-communicating cysts with thin septations that lack solid components or necrosis.
  - **These lesions often "herniate" or protrude into the renal pelvis producing either hemorrhage or urinary obstruction**.[3]
  - Histologic findings of hobnail epithelium and fibrous septa without malignant elements confirm the diagnosis.
  - Unlike pediatric cystic nephroma, there is no association with DICER1 mutations[32]
- **Mixed epithelial and stromal tumor** (MEST) of the kidney is an uncommon neoplasm
  - Comprised of solid stromal components and cystic epithelial elements.
  - **All cases are reported in adults with a female preponderance particularly in those with a history of estrogen therapy**
  - Rare cares of malignant transformation have been described

1.4 Metanephric Tumors

- **Metanephric adenoma** occurs in children and adults in their 5th or 6th decades of life.
- Female preponderance is noted. Although 50% are incidentally discovered, **polycythemia may be a presenting laboratory finding**
- Considered to arise from maturation arrested embryonal rests due to resemblance to nephrogenic rests/maturing Wilm's tumor[33]
- Rare cases of co-existing renal cell carcinoma (RCC), sarcoma, or metastasis have been described.

Table 1. WHO Classification of Benign Renal Masses

Classification	Types
Epithelial Tumors	Oncocytoma Papillary adenoma
Mesenchymal Tumors[34]	Angiomyolipoma Leiomyoma Hemangioma Lymphangioma Juxtaglomerular cell tumor Renomedullary interstitial cell tumor (medullary fibroma) Reninoma Schwannoma Lipoma
Mixed Epithelial and Stromal **Tumors**	Mixed epithelial and stromal tumor Cystic nephroma
Metanephric Tumors	Metanephric adenoma Metanephric adenofibroma Metanephric stromal tumor

2. Hereditary Kidney Cancer Syndromes

There are at least four well-described hereditary clinical kidney cancer syndromes with age of onset of approximately 46 years or younger being a potential sign of hereditary RCC (**Table 2**).[35] All are **autosomal dominant**.[36] **Genetic evaluation is recommended for patients presenting with a renal tumor before 46 years of age or if they have a significant family history for malignancy.**

2.1 Von Hippel-Lindau Syndrome (VHL)

- **Clear cell RCC** develops with early age of onset (3rd - 5th decade) and is often **bilateral** and **multifocal** (approximately 50% penetrance).
- Clinical manifestations include **retinal angiomas, endolymphatic sac tumors, benign CNS hemangioblastomas, pancreatic cysts and islet tumors, epididymal cystadenomas, and pheochromocytomas.**
- A **mutated *VHL* tumor suppressor gene**, located at **chromosome 3p25-26**, is unable to form the E3 ubiquitin ligase complex which regulates the degradation of regulatory proteins, including Hypoxia Inducible Factor (HIF-1, HIF-2).[37]
- The resultant over accumulation of intracellular HIF results in upregulation of **vascular endothelial growth factor (VEGF)** and other regulatory proteins impacting cellular growth and development.[38]
- Belzutifan (HIF-2alpha inhibitor) has been FDA approved for use among patients with VHL syndrome based on an open label singl group phase II trial treating patients with VHL syndrome and RCC with 120mg of belzutifan daily[39]
    - 49% had an objective response in RCC tumors with a median follow-up of 22 months
    - Patient also had objective responses in non-RCC neoplasms (77% pancreatic lesions, 30% CNS hemangioblastomas)
    - Most common adverse event was anemia (90% of patients) and fatigue (66%)

2.2 Hereditary Papillary Renal Cell Carcinoma (HPRCC)

- Characterized by **bilateral and multifocal Type I papillary RCC**.
- Least common syndrome, and there are **no extrarenal findings**.
- Missense mutation of the ***c-MET* proto-oncogene at 7q31**.[40]

2.3 Hereditary Leiomyoma Renal Cell Carcinoma (HLRCC)

- Characterized by **fumarate hydratase deficient RCC tumors (previously called papillary type II)** (20% penetrance), with an aggressive clinical behavior necessitating early surgical intervention with wide resection. Metastatic progression is not uncommon.
- Other clinical manifestations include **painful cutaneous and uterine leiomyomas**.
- The HLRCC locus has been mapped to **1q43**, the site of the ***Fumarate Hydratase*** tumor suppressor gene.[41]

2.4 Birt-Hogg-Dube Syndrome (BHD)

- Characterized by **bilateral, multifocal, chromophobe RCC, oncocytomas, or hybrid renal tumors** (20-40% penetrance).
- Other clinical manifestations include **fibrofolliculomas of the head and neck, pulmonary cysts, and spontaneous pneumothorax**
- The *BHD* gene has been mapped to **17p11.2**, which encodes the tumor suppressor gene product ***Folliculin***.[42]

2.5 BAP1 Tumor Predisposition Syndrome

- Typically, **unifocal ccRCC**, but other histologies recently reported
- Other associated cancers include **uveal and cutaneous melanomas and mesotheliomas**
- The **BAP1 gene** has been mapped to **3p21.1**. Somatic loss is common in sporadic ccRCC and associated with high nuclear grade and more aggressive behavior.

2.6 Succinate dehydrogenase RCC

- Patients generally present with **unifocal tumors** characterized by neoplastic cells with vacuolated cytoplasm and cytoplasmic inclusions that contain pale eosinophilic fluid of flocculent material
- 4 genes encode the succinate dehydrogenase complex: SDHA (5p15), SDHB (1p36), SDHC (1q21), and SDHD (11q23). The syndrome is known to occur in all except SDHA.
- **Loss of SDHB** on immunohistochemistry (IHC) is a sensitive and specific marker for these neoplasms and should prompt genetic assessment (recognized WHO histology)
- Other associated tumors include **paragangliomas, pheochromocytomas and gastrointestinal stromal tumors**[43,44]

Table 2. Familial Renal Cell Carcinoma Syndromes

Syndrome	Mechanism	Clinical Manifestations
Von-Hippel Lindau (VHL)	pVHL tumor suppressor gene (3p25-26)	Clear cell or cystic RCC Retinal angiomas CNS hemangioblastomas Pancreatic cysts and islet tumors Epididymal cystadenomas Pheochromocytomas
Hereditary Papillary RCC (HPRCC)	cMET proto-oncogene (7q31)	Type I papillary RCC
Hereditary Leiomyoma RCC (HLRCC)	Fumarate hydratase tumor suppressor gene (1q42-44)	FH-deficient RCC (aggressive) Cutaneous leiomyomas Uterine fibroids
Birt-Hogg-Dube (BHD)	Folliculin tumor suppressor gene (17p11.2)	Chromophobe RCC or oncocytomas Fibrofolliculomas of head and neck Pulmonary cysts and spontaneous pneumothoraces
BAP1 tumor predisposition syndrome	BRCA1 Associated Protein 1 (3p21.1)	Clear cell RCC or other Uveal and cutaneous melanomas Mesothelioma
Succinate dehydrogenase RCC	Succinate Dehydrogenase Complex (*SDHB, SDHC, SDHD)*	SDH-deficient RCC Paragangliomas Pheochromocytoma GIST

3. Renal Mass Biopsy (RMB)

The role of renal mass biopsy is expanded in contemporary practice. Identification of low risk and benign renal tumors may impact treatment decision-making especially in patients who are not ideal candidates for surgical treatment. For patients, who are considering thermal ablation or active surveillance, pathologic diagnosis with renal mass biopsy also may facilitate more informed shared decision-making.

3.1 Indications

- Renal mass biopsy (RMB) is discussed in the **Renal Mass and Localized Renal Cancer: Evaluation, Management, and Follow-Up: AUA Guideline (2021)**, which states:[45,46]
  - When considering the utility of RMB, patients should be counseled regarding rationale, positive and negative predictive values, potential risks ,and non-diagnostic rates of RMB
  - Clinicians should consider RMB when a mass is suspected to be hematologic, metastatic, inflammatory, or infectious. In the setting of a solid renal mass, RMB should be obtained on a utility-based approach whenever it may influence management. RMB is not required for 1) young or healthy patients who are unwilling to accept the uncertainties associated with RMB; or 2) older or frail patients who will be managed conservatively independent of RMB findings. For patients with a solid renal mass who elect RMB, multiple core biopsies should be performed and are preferred over fine needle aspiration.
  - A RMB should be performed prior to (preferred) or at the time of ablation to provide pathologic diagnosis and guide subsequent surveillance.

3.2 Accuracy

Contemporary experiences suggest accuracy rates of > 90% for malignant versus benign disease with improved sensitivity (80-92%) and specificity (83-100%);[47] low complication rates,[47] minimal risk of tract seeding (< 0.01%),[48] low false-negative rates (< 5%),[49] and low non-diagnostic rates (~10-15%) with repeat RMB following non-diagnostic biopsy yielding a diagnosis in 79.2-100%.[50,51,52] (**Table 3**) Risk factors for non-diagnostic biopsies include cystic features, contrast enhancement, mass diameter and skin-to-mass distance > 13 cm.[52] To minimize the risk of non-diagnosis, core biopsies should be obtained rather than relying on fine needle aspiration and some authors advocate for real-time pathology review at the time of RMB.

3.3 Limitations

- The most clinically relevant limitation of RMB is the underestimation or inability to differentiate low from high-risk malignancy by tumor grade given the limited sampling obtained and intratumoral heterogeneity.[53]
- Institutional experiences using core biopsy rather than fine needle aspiration techniques have reported that Fuhrman nuclear grading can be determined in 76-94% of cases, with accuracy rates ranging from 63-76%.[54]
- The role of biopsy to stratify prognosis, while under investigation, is not yet standard practice.
- Studies are ongoing to integrate molecular information from biopsy specimens into clinical algorithms in order to guide patient counseling and inform personalized decision-making.

Table 3. Contemporary Outcomes from Renal Mass Biopsy Series Using an 18 Gauge Needle Technique

		Accuracy (%)				
Series	**Number of Tumors**	**Diagnosis**	**Malignancy**	**RCC Subtype**	**Grade**	**Complications (%)**
Lebret et al.[55]	119	79	86	86	74*	0
Maturen et al.[56]	152	96	Sensitivity 97.7 Specificity 100	N/A	N/A	1.3
Shannon et al.[57]	235	78	100	98	N/A	0.9
Volpe et al.[48,49]	100	84	100	100	75*	1.0
Wang et al.[49]	110	90.9	100	96.6	N/A	1.8
Veltri et al.[58]	150	100	N/A	93.2	N/A	0
Leveridge et al.[59]	345	80.6	99.7		63.5	0.3
Richard et al.[60]	529	90; 94#	97	93	94*	8.5
Posielski et al.[51]	1155	85.6;97.2#	N/A	N/A	N/A	2.1
Deshmukh et al.[61]	226/1000@	78	97	92	76	N/A

Restricted to series with at least 100 biopsies performed for brevity

* classified as low (Fuhrman grade I/II) or high (Fuhrman grade III/IV)

diagnostic rate of repeat biopsy

@ series of 1000 biopsies, pathologic concordance with surgical specimen in 226.

4. Active Surveillance

Increased abdominal imaging has led to significant incidental detection of clinically localized renal masses.[62] However, despite a corresponding increase in tumors managed surgically, mortality rates from kidney cancer remain essentially unchanged. This implies that a proportion of small renal masses (SRMs) may represent over diagnosed benign or indolent tumors that do not require surgical intervention. Over the past decade, accumulating evidence has shown that active surveillance is a safe initial management strategy for select patients with a SRM. Current AUA guidelines support the use of AS in patients with a SRM <2cm or larger in patients with competing comorbidities.[45]

4.1 Definition

Serial radiographic imaging to define growth kinetics and guide the need for definitive intervention.

4.2 Indications

Active surveillance has been incorporated into the **Renal Mass and Localized Renal Cancer: AUA Guideline (2021)**, which states:[45,46]

1. For patients with a solid renal mass <2cm, or those that are predominantly cystic, **AS with potential for delayed intervention is an option for initial management.**
2. **Prioritize AS/Expectant Management when the anticipated risk of intervention or competing risks of death outweigh the potential oncologic benefits of active treatment.**
3. When the **risk/benefit analysis for treatment is equivocal and the patient prefers AS**, physicians should **repeat imaging in 3-months** to assess for interval growth and **may consider RMB for additional risk stratification**. Repeat cross sectional imaging should be obtained 3-6 months later.
4. **When the oncologic benefits of intervention outweigh the risks of treatment and competing risks of death, physicians should recommend intervention** In this setting, AS may be pursued only if the patient understands and is willing to accept the associated oncologic risk. Clinicians should encourage RMB for additional risk stratification. If the patient continues to prefer AS, close clinical and cross-sectional imaging with periodic reassessment and counseling should be recommended.

Table 4. Factors Favoring AS/Expectant Management

Patient Related	Tumor Related
Older age	Tumor size < 3 cm
Life expectancy < 5 years	Tumor growth < 5 mm/year
High comorbidity burden	Non-infiltrative
Excessive perioperative risk	Low complexity
Frailty/Poor functional status	Favorable histology
Patient preference for AS	Predominantly cystic
Marginal renal function	

4.3 Surveillance Protocols

- Currently there is no standardized protocol for active surveillance.
- **Following initial diagnosis, repeat imaging using the same modality should be performed within 3 to 6 months**
- **Periodic clinical/imaging surveillance can then be based on growth rate and shared decision making with intervention recommended if substantial interval growth or if other clinical/imaging findings suggest that the risk/benefit analysis is n longer equivocal or favorable for continued AS.**[45,46,63]
- Size comparisons should be performed using a **consistent radiographic characteristic** (most commonly maximum tumor diameter) while paying close attention to the cross-sectional cut from which the measurement is obtained.[64]
- Renal mass biopsy may be used for additional oncologic risk stratification. However, it is not indicated if it will not change management (for example, an older frail patient who will be managed conservatively regardless of results).[45,46]

4.4 Natural History

- Systematic review of large institutional experiences suggests that SRMs managed expectantly grow slowly (linear growth rate 0.13-0.7 cm/year) **Table 5**
- A substantial proportion of tumors (benign and malignant) demonstrate zero net growth (23-33%) over time.[65,66,67,68] however, both benign and malignant lesions can demonstrate non-zero growth rates.[66,69]
- Pathologic information has been reported for approximately 50% of tumors managed with AS with more than 90% confirmed malignant[70] however a large proportion of small renal masses represent indolent renal cell carcinomas, with increasing risk of more aggressive histology observed with increasing size.[71]

4.5 Clinical Outcomes and Triggers for Intervention

- In a systematic review of 28 AS studies which included cT1b masses, the rates of metastatic progression (1-6%) and cancer specific mortality (1-18%) were low while other cause mortality ranged from 0-45%.[8]
- In the prospective DISSRM (Delayed Intervention for Small Renal Masses) registry, the rate of crossover to definitive treatment wa 12.4% (46/371) at a median of 12 months. Median growth rate was higher (0.38 vs 0.05 cm/year) in the delayed intervention group
- Complex renal cysts (Bosniak III and IV) may also be observed with 67-month cancer specific and metastasis free survival of 99.7% and 99.1%.[73]
- Cancer-specific survival on AS with > 5 years follow-up is 99-100%.[74,75]
- Triggers for intervention may include size ≥ 4cm, accelerated growth rate (0.3-0.5cm/year), development of symptoms, or patient preference[75]
- Tumor growth rate, historically believed to be the most important factor associated with adverse pathology,[67] is associated with progression to treatment but not with cancer-specific death or metastatic progression.[74,68,72]
- Tumor size is likely the best predictor of oncologic outcomes[71]
- Delay to definitive treatment is safe and does not significantly impact the ability to perform minimally-invasive or nephron-sparing surgery.[76]

4.6 Limitations

- Data regarding the best triggers for intervention have not yet been defined
- Patients on active surveillance with biopsy-proven malignant tumors exhibit worse psychological distress following biopsy and at last follow up.[77]

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Table 5. Natural history of small renal masses managed with active surveillance

Study	Year Published	N (#Small Renal Masses)	Initial mean linear tumor diameter (cm)	Linear Growth Rate (cm/yr)	Follow Up (months)	Metastases N (%)
Kouba et al.[78]	2007	43 (46)	2.92	0.7	35.8	0
Siu et al.[79]	2007	41 (47)	2 (0.8-5)	0.27 (-0.13-1.5)	29.5	1 (2.4)
Abouassaly et al.[80]	2008	110	2.5* (0.9-11.2)	0.26 (0-3.3)	24	0
Beisland et al.[81]	2009	63 (65)	4.3 (1.3-11.1)	0.66 (-0.4-4.9)	33 (1-34)	2 (3.2)
Crispen et al.[82]	2009	154 (173)	2.45 (0.4-12)	0.29 (-1.4-2.47)	31 (12-156)	3 (1.9)†
Rosales et al.[83]	2010	212 (223)	2.8* (0.5-13.1)	0.34* (0.29-2.3)	35* (6-137)	4 (1.9)
Hwang et al.[84]	2010	46 (58)	2.1	0.21	22 (5-121)	0
Jewett et al.[85]	2011	127 (151)	2.1 (0.4-4.0)	0.13	28 (9-61)	2 (1.1)
Pierorazio et al[75]	2015	223	1.9	0.11	25.2 (10.8 -45.6)	0
McIntosh et al[74]	2018	457 (544)	2.1	0.19	67 (IQR 41-94)	8 (1.75)
Gupta et al[72]	2019	371	1.8	0.09 (median)	23.6 (9.0−43.4)	0

Restricted to institutional experiences with more than 40 patients for brevity

* median value, † includes, unpublished data

5. Localized Renal Cell Carcinoma

Renal cell carcinoma (RCC) originates from the **renal cortex** and constitutes the large majority (80-85%) of primary renal neoplasms. Other less common primary renal neoplasms include benign renal cortical tumors as discussed earlier, **urothelial carcinoma** of the ren pelvis, sarcomas, and **Wilms' tumor (more common in pediatric patients)**.

See AUA **Diagnosis and Management of Localized, Locally Advanced and Advanced Kidney Cancer Webcast (2022)**

5.1 Etiology

- RCC occurs predominantly in the 6th to 8th decades of life.
- More common in men.
- Approximately 79,000 new renal cancers (50,290 men and 28,710 women) and 13,920 deaths (8,960 men and 4,960 women) in the United States are expected in 2022[86]
- Risk factors associated with development of RCC include:
    1. Smoking[87]
    2. Hypertension[88]
    3. Obesity[89]
    4. Acquired renal cystic disease (papillary RCC most common)
    5. Occupational exposure (including cadmium, asbestos, and gasoline)[90]
    6. Genetics (including germline variants in *VHL*, *MET*, *FH, TSC1/2*, *FLCN*, *SDHA*/*B*/*C*/*D*, *BAP1*, *MITF* genes)[91]

5.2 Histologic Classification of RCC

- **Clear cell RCC**:
    - Most common RCC histology.
    - Arises from **proximal convoluted tubule**.
    - Associated with **loss of 3p** which is also seen in VHL syndrome.
- **Papillary RCC**:
    - Arises from **proximal convoluted tubule**.
    - The World Health Organization (WHO) 2022 classification eliminated the type ½ papillary RCC subcategorization[92]
    - **Papillary RCC** is associated with **polysomy 7 and 17, loss of Y, and MET mutations**
    - May be **bilateral**, even in non-familial cases.
    - Can be associated with hereditary papillary RCC **(HPRCC)** syndrome
- **Chromophobe RCC:**
    - Histologically similar to oncocytoma.
    - Arises from **collecting duct.**
    - Common mutations in ***TP53 and PTEN***.
    - Can be associated with Birt-Hogg-Dube syndrome.
    - Is not assigned a histologic grade[93]
- **Collecting duct carcinoma:**
    - Rare and aggressive, with poor prognosis.
    - Arises from **collecting duct.**
- **Renal medullary carcinoma:**
    - Rare and most aggressive form of RCC. Median survival of 13 months[94]
    - Loss of SMARCB1/INI1[95] which is linked to c-MYC overexpression[96]
    - Occurs in **young African American adults with sickle cell trait.**[97]
- **Fumarate hydratase-deficient RCC**
    - Previously classified as type 2 papillary RCC now constitute independent category[92]
    - Aggressive histology, frequently presented with metastatic disease
    - IHC staining showed **loss of FH expression** and **2SC positive**
    - Associated with **hereditary leiomyomatosis and renal cell cancer syndrome (HLRCC)**
- **Succinate dehydrogenase-deficient RCC**
    - IHC staining showed loss of SDHB
    - Associated with **hereditary paraganglioma/pheochromocytoma syndrome**
- **Microphthalmia associated transcription factors (MiT) family translocation RCC**
    - **Includes Xp11 translocation, TFE3 rearrangement, TFEB arrangement or amplification**
    - More common in children and young adults

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- Prognosis:[90,98,99]
  - Clear cell considered among the more aggressive of the common histologies while papillary and chromophobe are generally more indolent.
  - Histologic nuclear grade of tumor is associated with oncologic risk of progression and recurrence.
  - Mixed renal tumors can occur in up to 5% of cases with prognosis dictated by more aggressive subtype.[100]

5.3 Presentation

- In contemporary practice, the classic triad of flank mass, hematuria, and pain is infrequently (< 10%) encountered.
- Contemporary studies report that **most renal masses are discovered incidentally** likely secondary to increased utilization of axia cross-sectional imaging which is supported by **stage migration** trends for kidney cancer with increasing proportions of patients being diagnosed with a small renal mass.[101]
- Despite the increased discovery of incidental renal masses, the **incidence of metastatic disease at presentation remains 30% across population-based studies**.
- **Paraneoplastic syndromes** associated with RCC include:
  - **Stauffer's syndrome:** Reversible hepatitis not associated with liver metastases (non-metastatic hepatic dysfunction).
  - **Constitutional symptoms**: fever, chills, weight loss, cachexia.
  - Anemia or Polycythemia.
  - **Elevated erythrocyte sedimentation rate, C-reactive protein, alkaline phosphatase, and calcium**.
- The **malignancy risk of a renal tumor as well as its metastatic likelihood (if cancer) are both strongly associated with tumo size**[102,103]

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Table 6. Risk of Metastases and Harboring RCC at Presentation*

Tumor Size	% Benign Pathology	% M1 RCC
< 1 cm	35-45%	< 1%
1 cm-2 cm	20-25%	< 1%
2 cm-3 cm	15-20%	< 1%
3 cm-4 cm	15-20%	2%
4 cm-5 cm	˜10%	2-3%
5 cm-6 cm	˜10%	5-10%
6 cm-7 cm	˜5%	5-10%
> 7 cm	˜5%	15-20%

* *The data presented represents a surgical series and patients who presented to urologic surgeons. Therefore, the true incidence of metastatic disease based on renal tumor size may be higher than reported.*

5.4 Treatment of Localized RCC

- The TNM staging for RCC according to the American Joint Committee on Cancer is depicted in **Table 7**.
- The updated 2021 AUA Renal Mass and Localized Renal Cancer: Evaluation, Management, and Follow-up guideline provide a framework for management.
- **Patients with localized kidney cancer typically do not die of kidney cancer** thereby underscoring the importance of preservation of renal function and considering survivorship issues.[41] This is particularly true for older patients with competing risks o mortality.[104]
- The management of specific clinical scenarios are outlined below per the AUA guidelines.
- **Features predictive of outcome after surgical treatment of localized RCC include T stage, tumor size, nuclear grade, presence of histologic necrosis, and performance status**[105,106]
- There are several different prognostic systems for kidney cancer outcomes including (but not limited to) the SSIGN, UISS, Leibovich, and MSKCC models. All use an amalgam of clinical and tumor characteristics to provide a prediction of disease outcomes. For example, the **SSIGN** (Stage, Size, Grade, and Necrosis) score is an externally validated algorithm used to predict outcome for patients with clear cell RCC.[105,107,108,109] Other validated prognostic systems include the UISS, Leibovich, and MSKCC systems.
- Initial evaluation of a solid or cystic renal mass should include
  - **CT or MRI with and without contrast (renal protocol)** if patient's renal function is adequate to receive iodinated contrast
  - **Chest X-ray** or chest CT without contrast (preferred)
  - Advanced imaging including **nuclear medicine bone scan** and brain **MRI** as clinically indicated (Note: **PET CT is not recommended in the evaluation of a suspected renal malignancy**)
    - New molecular imaging modalities under investigation may help to differentiate between malignant and benign renal tumors
      - **Sestamibi SPECT scan** – sestamibi is a lipophilic cation that accumulates in cells with high mitochondrial content such as oncocytes. As a result, sestamibi scan has been used to distinguish benign oncocytoma from RCC
        - Oncocytoma has high uptake of tracer (appear "hot") while RCC has low tracer uptake (appear "cold).
        - The sensitivity and specificity of ^{99m}Tc-sestamibi SPECT/CT in identifying oncocytoma were 88% and 95%, respectively[9]
      - **Carbonic anhydrase IX (CAIX)-targeted PET scan** – CAIX is highly expressed in clear cell RCC. ^{124}I-girentuxima PET, which targets CAIX, showed promising results in identifying clear cell RCC in preoperative setting.[110,111]
      - **Prostate Specific Membrane Antigen (PSMA) PET scan** – even though the vast majority of PSMA imaging has been used in prostate cancer, PSMA is also overexpressed in neovasculature of some solid tumors such as RCC.
        - The role of PSMA PET in localized renal tumor imaging is unclear.
        - The most promising application of PSMA PET may be in differentiating clear cell and non-clear cell RCC histologies in metastatic setting to determine therapy.[113]
  - Laboratory work including complete blood count, comprehensive metabolic panel, and urinalysis.
  - Assignment of baseline CKD stage based on glomerular filtration rate (GFR) and degree of proteinuria (**Table 8**).
  - o If urothelial carcinoma if suspected: consider cystoscopy, ureteroscopy with biopsy if feasible, urine cytology as appropriate
- **Management of cystic renal mass**
  - **Bosniak classification** is used to characterized complex renal cysts and requires multiphase CT or MRI of the abdomen (ultrasound is not used to determined Bosniak classification)[114]
    - The Bosniak Classification was updated in 2019 and incorporated MRI findings into the classification[114]
    - **Bosniak I/II cysts** do not require follow up
    - **Bosniak IIF cysts**: the majority are benign or indolent and rarely require intervention. Follow up at 6 months and 12 months then annually for up to 5 years.
    - **Bosniak III/IV cysts**: patient counseling and management decision need to take into consideration baseline CKD, degree proteinuria, patient's comorbidities/frailty, and life expectancy
      - Surgery with either partial or radical nephrectomy based on the tumor size and complexity if intervention is deeme necessary
- **Genetic counseling is recommended for the following patients**[45]
  - **All patients with age of diagnosis of RCC ≤ 46 years**[35,115]
  - **All patients with multifocal or bilateral renal masses**
  - Personal or family history suggestive of a hereditary kidney cancer syndrome
  - 1st or 2nd degree relative with known diagnosis of RCC or known clinical or genetic diagnosis of hereditary kidney cancer syndrome

of

ab

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d

- **Patient’s pathology suggestive of an underlying syndrome** (e.g., FH-deficient or SDH-deficient RCC)

Table 7. TNM staging system for RCC; Adopted from the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th Edition (2017), Springer New York Inc.93

Classification	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 7cm or less in greatest dimension, limited to the kidney
T1a	Tumor 4cm or less in greatest dimension, limited to the kidney
T1b	Tumor more than 4cm but not more than 7cm in greatest dimension, limited to the kidney
T2	Tumor >7cm in greatest dimension, limited to the kidney
T2a	Tumor >7cm and ≤ 10cm in greatest dimension, limited to the kidney
T2b	Tumor >10cm in greatest dimension, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
T3a	Tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota's 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's fascia (including contiguous extension into the ipsilateral adrenal gland)
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
Distant metastasis (M)	

M0	No distant metastasis
M1	Distant metastasis
Anatomic Stage Groups	
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T1 or T2 N1 M0 T3 Nx or N0 or N1 M0
Stage IV	T4 Any N M0 Any T Any N M1

5.5 Partial Nephrectomy (PN)

- **PN or nephron sparing surgery (NSS)** consists of removal of the tumor with a **negative surgical margin** followed by renal reconstruction (**renorrhaphy**). This can be accomplished via open, laparoscopic, or robotic-assisted laparoscopic approaches.
- **Oncologic success is comparable to radical nephrectomy** for clinical T1a and T1b renal masses, and select T2 renal tumors.[116,117]
- PN should be prioritized as management strategy of choice when intervention is needed for cT1a and select cT1b renal masses.
- PN should be **prioritized** in patients with an **anatomic or functional solitary kidney, bilateral renal tumors, known familial RCC, preexisting CKD, and proteinuria**
- PN should be **considered** for patients who are **young, have multifocal masses, or have comorbidities that may impact kidne** function **in the future**.
- Anatomical characterization of renal masses for descriptive purposes can be described using nephrometry indices which communicate the location of the tumor with respect to the collecting system and hilar anatomy, and communicate the exophytic vs. endophytic nature of the tumor (**RENAL**, **PADUA**[118], **C-index**[119]).[120]
- Open PN has long been considered the optimal approach to PN. More recently, laparoscopic and subsequently robotic PN approaches are increasingly utilized[121,122] with equivalent oncologic and functional outcomes when performed by experienced surgeons.
- The main benefit of PN is **preservation of renal function** while achieving equivalent oncologic control compared with radical nephrectomy.[123]
- The **primary determinants of long-term renal function after PN are preoperative renal function, ischemia duration, comorbidities, and amount of preserved kidney** (e.g., residual functional renal parenchyma).[124]
- **Ischemia time** is a modifiable feature predictive of long-term renal function and should ideally be limited.[125,126,127,128]
- Cold ischemia with ice slush allows for longer tolerated ischemia times which can facilitate nephron-sparing approaches in cases o endophytic, hilar, interpolar, and large tumors as well as in cases with complex tumors in solitary kidneys.[124,129]
- Owing to preservation of renal function with PN, retrospective and propensity matched observations suggest improved overall survival of PN compared with RN.[130,131] **Nonetheless, a randomized controlled trial (EORTC 30904) failed to support this conclusion in patients with tumors less than 5 cm**[117] **Notable trial limitations included a 1) high degree of loss of follow-up 2) cross-over between arms; and 3) early closure due to poor accrual, resulting in the study being underpowered for planned conclusions**

Table 8. Stages of chronic kidney disease

Stage	Classification	Classification
I	90+	Normal kidney function
II	60 - 89	Mildly reduced kidney function
III IIIa IIIb	30 - 59 45 - 59 30 - 44	Moderately reduced kidney function
IV	15 - 29	Severely reduced kidney function
V	< 15 or on dialysis	End stage renal disease

5.6 Radical Nephrectomy (RN)

- For **healthy patients: RN is an alternate standard of care if PN is not technically feasible for cT1a renal masses and is a standard of care for cT1b or larger renal masses in the setting of a normal contralateral kidney**, although PN can also be performed in selected patients in this group.
- RN may be the preferred modality for higher risk kidney tumors provided the following are met:
  - High tumor complexity (endophytic, hilar tumor, interpolar, large tumor) and PN would be challenging in experienced surgeons' hands.
  - No existing CKD or proteinuria.
  - Normal contralateral kidney with anticipated post-operative GFR > 45.
- Compared with PN, **RN has a lower rate of complications**[132] including hemorrhage (1.2% vs 3.1%), urine leak/fistula (0% vs 4.4%), and re-operation for complications (2.4% vs 4.4%) based on data reported in the EORTC 30904 phase III randomized trial.[13]
- **RN increases the risk of CKD** compared with PN.[88,130,134]
- **Removal of the adrenal gland during RN is only indicated for clinical suspicion of involvement based on preoperative imaging (suspected local invasion and/or metastasis) and intraoperative findings**.[135] The incidence of ipsilateral adrenal involvement in patients with RCC is less than 10%. **Risk factors associated with adrenal gland involvement include CT evidence of tumor invasion into the adrenal gland, tumor size > 5 cm, and upper pole location, although the latter two are not necessarily indications for adrenalectomy**
- Regional lymph node dissection does not improve cure rate or survival in patients with low stage, localized RCC based on results the EORTC 30881 phase III randomized trial.[136] However, **a lymph node dissection improves staging in patients with clinical suspicion of positive nodes**, albeit with the potential for added complications.[137]

5.7 IVC thrombectomy

- **Venous tumor invasion is present in up to 10% of RCC tumors**.[138] Tumor thrombus is less common in other renal tumors but has also been reported in upper tract urothelial cancers, Wilm's tumors and oncocytic renal tumors.[139] Patients with metastatic RCC may have a higher incidence of venous tumor thrombus.[140]
- During the initial evaluation of a renal mass, physicians should evaluate for suspicion for vascular invasion.
  - **Magnetic resonance imaging (MRI) or computed tomography** (CT) are used for evaluation of the extent of venous invasion.[139,140]
  - Arteriogram, abdominal ultrasound, and echocardiography may also be helpful imaging techniques to characterize upper leve IVC thrombus.
- RCC associated "thrombus" is generally composed of tumor alone or a combination of tumor and bland thrombus.[141] The presence of bland thrombus may be associated with disrupting vascular flow[142] and is associated with worse postsurgical outcomes.[143]
- The extent of venous invasion is variable, with some tumors invading into the venous system and terminating within the branches o the renal veins while other tumors extend into the inferior vena cava (IVC) and into the heart. Worse outcomes with increased degrees of tumor venous invasion have long been recognized as prognostic for cancer outcomes and reflected in the American Joint Committee on Cancer (AJCC) staging protocol.[144]
- Multiple systems are available to describe the extent of tumor thrombus in the venous system.[145]
- In the eighth edition AJCC staging manual,[144] venous invasion is classified by the T stage according to the extent of invasion as described below:
  - **T3a tumor grossly extends into the renal vein or its segmental (muscle containing) branches**
  - **T3b tumor grossly extends into the vena cava below the diaphragm**
  - **T3c tumor grossly extends into the vena cava above the diaphragm**
- However, the **Neves Zincke** classification is more useful from a technical surgical approach:[146]
  - **Level 0: Tumor thrombus limited to renal vein**
  - **Level 1: Extending ≤2 cm above the renal vein**
  - **Level 2: Extending >2 cm above the renal vein but below the hepatic veins**
  - **Level 3: At or above the hepatic veins but below the diaphragm**
  - **Level 4: Extending above the diaphragm**
- In patients without metastatic disease, nephrectomy with IVC thrombectomy is associated with 5-year recurrence-free survival rate of approximately 50%. Independent **predictors of recurrence after surgery include larger tumor diameter, lower body mass index, preoperative hemoglobin less than the lower limit of normal, higher thrombus level, perinephric fat invasion and non-clear cell histology**[147]
- Similar postsurgical outcomes can be expected for patients who have thrombus in the renal vein only or thrombus terminating in th

IVC below the hepatic veins after complete surgical excision.[147,148]

- In contemporary multi-institutional series, worse oncologic and perioperative outcomes have been demonstrated for RCC patients with extension of tumor into the IVC thrombus above the hepatic confluence of veins, compared with lower-level thrombus patients.[147,149,150]
- Surgery for patients with kidney tumors with venous invasion is complex and associated with higher risk of perioperative complications. In non-metastatic patients, the goal of surgery is to remove all tumor including thrombus. A **multidisciplinary approach** is helpful for IVC thrombectomy and may include involvement of surgeons from other teams including vascular surgery, hepatobiliary surgery, surgical oncology or cardiothoracic surgery.[151] Better outcomes have been demonstrated at higher volume centers, which highlights the importance of an experienced surgical team.[152]
- In order to safely incise the IVC, all sources of venous inflow must be temporary occluded to provide visualization so the thrombus can be completely removed.
- **Prior to IVC thrombectomy vascular occlusion should include**:
  - **Renal artery supplying the affect kidney with tumor thrombus**
  - **Infrarenal IVC below thrombus**
  - **Lumbar veins feeding in to the IVC**
  - **Contralateral renal vein**
  - **Hepatic blood supply** for thrombus that extends about the hepatic veins. A **Pringle maneuver** is performed to decreased hepatic blood flow by placing a clamp across the hepatic artery and portal vein (portal triad) within the hepatoduodenal ligament. This is mainly done for level 3 or higher tumor thrombus.
  - **Suprarenal IVC above the thrombus (which may entail the suprahepatic IVC)**
- The tumor thrombus may be free floating within the IVC or invasive into the IVC wall. When tumor thrombus is free floating within the IVC, the thrombus may be manually reduced and the IVC primarily repaired. When **thrombus is invasive into the wall of the IVC, tumors are classified as T3c because of the association with worse outcomes**.[153] Invasion into the wall of the IVC may b difficult to identify prior to surgery but is more likely with larger diameter of thrombus in the IVC or at renal vein ostium[154] or when complete IVC obstruction is suspected.[155] To remove all tumor in these patients, **resection of the IVC wall may be necessary**. Reconstruction of the IVC with a **vascular patch or tube graft**[156] may be necessary. **Complete excision and ligation of the IVC** may be performed in settings of complete occlusion of the IVC where there are extensive collateral veins, which may be advantageous especially when patients have extensive bland thrombus in the IVC caudal to the tumor thrombus.[157]
- IVC thrombectomy[158] for advanced renal tumors is a technically complex procedure, with higher risk of complications compared to typical radical nephrectomy at experienced centers.[159] Although rare, **one potentially fatal complication of thrombectomy that should be discussed prior to surgery is an approximately 1-2% risk for intraoperative embolization of thrombus causing obstruction of pulmonary arteries**[160]
- Transesophageal ultrasound may be used intraoperatively to 1) evaluate the superior extent of the tumor, 2) provide feedback regarding properties of the thrombus (e.g. fragility, adherence), 3) monitor cardiovascular status and fluid status, 4) to guide vascular clamp placement, 5) ensure complete removal of the tumor thrombus, 6) evaluate for real time embolization of the thromb
- Open surgical approach is preferred by most surgeons to achieve precise vascular control in the majority of patients. Laparoscopic nephrectomy with thrombectomy has been described in a small series of RCC patients with mobile lower level IVC thrombus.[162] Mor recently, a robotic-assisted laparoscopic approach has been reported to be feasible for selected patients at experienced centers.[163]
- Management of IVC tumor thrombus that extends above the diaphragm into the heart, may require additional surgical maneuvers t successfully remove the entire thrombus. **Cardiopulmonary bypass** (with or without hypothermic cardiac arrest) and **venovenou bypass**[164] are commonly used[165] to expose the cephalad extent of the tumor thrombus for resection. Alternatively, incising the diaphragm and pericardium from the abdomen may allow exposure of the cephalad extent of atrial thrombus avoiding cardiopulmonary bypass.[166] There are few data comparing outcomes among techniques, and the choice of approach will depend on the surgical and institutional expertise.

5.8 Ablation

See Update Series Vol 39 Lesson 38[167]

- Thermal ablation is an **option for cT1a renal masses, ideally ≤ 3 cm in diameter**.
- Tumor ablation can be accomplished through open, laparoscopic, or **percutaneou**s (most common) approaches and most commonly involve **radiofrequency**, **cryoablation**, or **microwave** ablation. Whenever feasible, a percutaneous approach is preferred owing to lower treatment-related morbidity.
- Long-term success rates are favorable at centers of excellence. A recent meta-analysis of 107 studies comparing thermal ablation to PN and RN demonstrated that **local recurrence-free survival was inferior for thermal ablation with 1 treatment but reache equivalence to other modalities after multiple treatments while overall survival was similar among management strategie and varied with age and comorbidity** Partial nephrectomy showed the highest rates of urological complications, but overall rates

of minor/major complications were similar across interventions.[168]

- **There is an increased risk of complications with centrally-located tumors, and tumors near the ureter or other organs** (e.g pancreas, diaphragm, spleen). The risk of such complications may be reduced by gas or liquid dissection and pyeloperfusion[169]
- The AUA guidelines recommend **core tumor biopsy** and **careful pretreatment discussion** regarding potentially higher risk of local recurrence, potential need for repeat intervention, need for long term abdominal imaging, and potential for difficult surgical salvage.[45] Core biopsy is preferred to fine needle aspiration.
- Renal function after ablation may be superior to PN given the absence of global renal ischemia from surgical clamping.[136]

5.9 Post-treatment Follow-up for Localized Kidney Cancer

- AUA guidelines on follow-up of clinically localized RCC are available and accessible on the AUA website: https://www.auanet.org/guidelines/guidelines/renal-mass-and-localized-renal-cancer-evaluation-management-and-follow-up#x154[45,46,108]
- Clinicians should classify patients managed by PN or RN for histologic kidney cancer into one of 4 risk groups: Low Risk (LR), Intermediate Risk (IR), High Risk (HR), Very High Risk (VHR). Imaging follow-up with abdominal cross-sectional imaging (CT or MRI) should be performed in an algorithmic manner based on risk group.

Table 9: Risk stratification after intervention[45,46]	
Low Risk (LR):	pT1 and Grade 1/2
Intermediate Risk (IR):	pT1 and Grade 3/4, or pT2 any Grade
High Risk (HR):	pT3 any Grade
Very High Risk (VHR):	pT4 or pN1, or sarcomatoid/rhabdoid dedifferentiation, or macroscopic positive margin

- Imaging intensity may be further modulated after 5 years based on shared decision making with the patient.
- The AUA guidelines have extended follow-up for up to 10 years based on retrospective that data suggest that extended surveillance (beyond 3 or 5 years) is needed to detect all recurrences.[70]
- **Table 10** Recommended follow-up schedule after surgery for renal cancer (in months)[45,46]

Table 10: Recommended follow-up schedule after surgery for renal cancer (in months)

Risk	3	6	9	12	18	24	30	36	48	60	72-84	96-120
LR				X		X			X	X	X	X
IR		X		X		X		X	X	X	X	X
HR		X		X	X	X	X	X	X	X	X	X
VHR	X	X	X	X	X	X	X	X	X	X	X	X

5.10 Adjuvant Therapies for High-risk Localized Kidney Cancer

See Update Series Vol 38 Lesson 19 [171]

- **Adjuvant therapies FDA-approved or under investigation for high-risk localized kidney cancer** can broadly be grouped into categories including: **1) VEGF and mTOR pathway inhibitors; 2) antibody-dependent agents; and 3) immune checkpoint inhibitors**[172]
- Risk-stratifying patients at greatest risk of recurrence following surgery will identify those at greatest likelihood of benefiting from adjuvant therapies. Nomograms (i.e., MSKCC, UISS, SSIGN) may help in this risk stratification.
- Several completed or ongoing adjuvant kidney cancer trials have explored the benefit of systemic therapies following nephrectomy .
- There are 2 FDA approved agents in the adjuvant setting: the PD-1 inhibitor pembrolizumab and the VEGF inhibitor sunitinib. Summaries of the trials below:
  - **KEYNOTE-564**:[173] Safety and Efficacy Study of Pembrolizumab (MK-3475) as Monotherapy in the Adjuvant Treatment of Renal Cell Carcinoma Post Nephrectomy. (NCT03142334)
    - Phase III randomization of 950 patients
    - Eligibility criteria: clear cell carcinoma pT2G4; pT3; pT4; pTxN+; M1 resected to NED within 1 year of nephrectomy
    - **Pembrolizumab** 200mg IV q3 week for 1 year versus **placebo**
    - **The study is the first positive study of an immune checkpoint inhibitor in adjuvant therapy for RCC and showed that pembrolizumab was associated with significantly longer disease-free survival than placebo**(DFS at 24 months, 77.3% vs. 68.1%; hazard ratio for recurrence or death, 0.68). Pending OS data.
  - **S-TRAC**[174]
    - Randomized, double-blind, phase 3 trial of 615 patients
    - Eligibility criteria: clear cell carcinoma pT3 or higher; pTxN+;
    - **Sunitinib** (50 mg per day) versus **placebo** on a 4-weeks-on, 2-weeks-off schedule for 1 year
    - Result: **Improved DSS was observed in the sunitinib arm**: the median duration of disease-free survival was 6.8 years (95% confidence interval [CI], 5.8 to not reached) in the sunitinib group and 5.6 years (95% CI, 3.8 to 6.6) in the placebo group (hazard ratio, 0.76; 95% CI, 0.59 to 0.98; P=0.03). **No difference in OS although study not powered for this analysis**.[175]
- VEGF and mTOR Inhibitor trials:
  - **ASSURE**[176]
    - Double-blind, placebo-controlled, randomized, phase 3 trial. Enrolled 1,943 patients with pathological stage high-grade T1b or greater with completely resected non-metastatic renal-cell carcinoma. Patients were randomly assigned (1:1:1) to receive 54 weeks of **sunitinib** 50 mg per day orally throughout the first 4 weeks of each 6-week cycle, **sorafenib** 400 mg twice per day orally throughout each cycle, or **placebo**.
    - Result: The primary analysis showed **no significant differences in disease-free survival.** Median disease-free survival was 5.8 years for sunitinib (p=0.8), 6.1 years for sorafenib (p=0.7), and 6.6 years for placebo.
  - **PROTECT**[177]
    - A study to evaluate Pazopanib as an Adjuvant Treatment for Localized Renal Cell Carcinoma.
    - 1,538 patients with resected pT2 (high grade) or ≥ pT3, including N1, clear cell RCC were randomly assigned to **pazopanib** or **placebo** for 1 year.
    - Result: The primary intention-to-treat analysis results of **disease-free survival favored pazopanib but did not show a significant improvement over placebo** (hazard ratio [HR], 0.86; 95% CI, 0.70 to 1.06; P = .165).
  - **ATLAS**[178]
    - Adjuvant Axitinib Therapy of Renal Cell Cancer in High Risk Patients
    - Prospective, randomized, double blind placebo-controlled trial of 724 patients with clear cell RCC pT3, pT4, or N+ randomized to oral **axitinib** 5mg twice daily for 3 years versus **placebo**.
    - **Trial stopped due to futility** at a preplanned interim analysis at 203 DFS events. **No significant difference in disease-free survival** [hazard ratio (HR) = 0.870; 95% confidence interval (CI): 0.660-1.147; P = 0.3211).
    - In the highest-risk subpopulation, a 36% and 27% reduction in risk of a DFS event (HR; 95% CI) was observed per investigator (0.641; 0.468-0.879; P = 0.0051), and by IRC (0.735; 0.525-1.028; P = 0.0704), respectively.
  - **SORCE**[179]
    - Sorafenib in Treating Patients at Risk of Relapse Undergoing Surgery to Remove Kidney Cancer (NCT00492258)
    - Randomized, placebo-controlled, double-blind, open-label, multicenter study
      - 1656 patients with intermediate or high risk RCC (Leibovich score 3-11) randomized to one of 3 treatment arms:
        - **Placebo** for 3 years

- **Sorafenib** 400mg twice daily for 1 year followed by **placebo** for 2 years
- **Sorafenib** 400mg twice daily for 3 years

- Result: No differences in DFS or overall survival in all randomly assigned patients, patients with high risk of recurrence, or patients with clear cell RCC only. Median DFS was not reached for 3 years of sorafenib or for placebo (hazard ratio, 1.01; 95% CI, 0.83 to 1.23; P = .95). Over half of participants stopped treatment by 12 months.[179]

- **EVEREST**
  - Everolimus in Treating Patients with Kidney Cancer who have Undergone Surgery
  - Phase III randomized trial of 1545 patients intermediate high-risk or very high-risk disease (pT2-pT4, pTxN+, pT1b G3/G4) receiving **everolimus** 10mg daily versus **placebo** once daily on days 1-42 with treatment repeating every 6 weeks for 9 courses in the absence of disease progression or treatment toxicity.
  - Result: Event rate lower than anticipated. RFS everolimus as compared to placebo (HR 0.85, 95% CI, 0.72 – 1.00; 1-sided p=0.0246). This failed to meet the pre-specified, one-sided significance level of 0.022.[180]
  - There were gender and age-related differences in everolimus trough levels in patients receiving adjuvant treatment for RCC. There were significant associations between everolimus exposure and probability of toxicity.[181]

- **Antibody-Mediated Cytotoxic Agents**
  - **ARISER**[182]
    - Adjuvant Rencarex Immunotherapy Phase 3 Trial to Study Efficacy in non-Metastatic Renal Cell Carcinoma (NCT00087022)
    - Randomized, double-blind, placebo-controlled trial. 864 eligible adult patients had undergone partial or radical nephrectomy for histologically confirmed ccRCC for pT3/pT4Nx/N0M0 or pTanyN+M0 or pT1b/pT2Nx/N0M0 with nuclea grade 3 or greater. Patients randomized to receive either a single loading dose of **girentuximab**, 50 mg (week 1), followed by weekly intravenous infusions of girentuximab, 20 mg (weeks 2-24), or **placebo**.
    - Result: Compared with placebo, participants treated with girentuximab had **no statistically significant DFS** (hazard ratio, 0.97; 95% CI, 0.79-1.18) or **OS advantage** (hazard ratio, 0.99; 95% CI, 0.74-1.32).
- **Immune Checkpoint Inhibitors**
  - **IMmotion010**: A Study of Atezolizumab as Adjuvant Therapy in Participants with Renal Cell Carcinoma at High Risk of Developing Metastasis following Nephrectomy (NCT03024996)
    - Phase III randomized trial of 778 patients receiving **atezolizumab** 1200 mg IV infusion every 3 weeks (q3w) for 16 cycles (each cycle=21 days) or 1 year (whichever occurs first) compared to **placebo**.
    - Eligibility criteria: Clear cell or sarcomatoid RCC pT2G4; pT3aG3-4; pT3b/cT4; pTxN+;M1
    - Primary endpoint DFS; estimated completion 2024.
  - **PROSPER**: Nivolumab in Treating Patients with Localized Kidney Cancer Undergoing Nephrectomy NCT03055013
    - Randomized trial of neoadjuvant **nivolumab followed by surgical treatment and additional adjuvant nivolumab** compared to standard of care **surgical treatment** followed by **observation**.
    - Phase III randomized of 805 patients
    - Eligibility; Any histology; cT2-pT4; cTxN+;M1a
    - Nivolumab 240mg x 1 dose prior to surgery; adjuvant x 9 months versus placebo (Nivolumab arms must have biopsy-proven disease)
    - Estimated completion 2023
  - **CHECKMATE 914**: A Study Comparing Nivolumab, Nivolumab in Combination With Ipilimumab and Placebo in Participants With Localized Kidney Cancer Who Underwent Surgery to Remove Part of a Kidney (NCT03138512)
    - Phase III randomization of 800 patients
    - Eligibility: Clear cell histology; pT2aG3/G4; pT2-pT4; pTxN+
    - **Nivolumab + ipilimumab** versus **nivolumab** versus **placebo** x 6 months
    - Estimated completion 2023
  - **RAMPART** Renal Adjuvant MultiPle Arm Randomised Trial (NCT03288532)
    - Phase III randomization of 1750 patients
    - Eligibility: Leibovich score 3-11; any histology
    - **Durvalumab** 1500mg q4 week versus **Durvalumab** 1500mg q4 week + **tremelimumab** 75mg day 1 and week 4 versu **placebo**
    - Estimated completion 2034.

6. Metastatic Renal Cell Carcinoma

Approximately **20-40% of patients with localized disease will eventually develop distant metastasis after nephrectomy**.[183] In addition, about **1/3 of patients diagnosed with kidney cancer present with metastatic disease**. Patients with advanced RCC presen

with a wide spectrum of disease varying from indolent to rapidly progressing. The majority of these patients are candidates for systemic therapy.

6.1 Prognostic Models

- Prognostic factors are instrumental for the purposes of clinical trial design, risk-stratified therapy and counseling of patients with metastatic renal cell carcinoma (mRCC).
- The **Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic model** is one of the first and most widely used prognostic models. It was developed using **pooled data from patients in clinical trials treated with INTERFERON ALPHA** from 1982-1996 **A KPS < 80%, a diagnosis of RCC to systemic treatment interval < 12 months, anemia, elevated LDH and hypercalcemia** were all independent predictors of **overall survival**.[184,185]
  - Patients in the favorable-risk group have zero factors (median OS, 29.6 months), intermediate-risk group have one or two risk factors (median OS, 13.8 months), poor-risk group have three or more risk factors (median OS, 4.9 months).
- **The International mRCC Database Consortium (IMDC) prognostic model** retrospectively collected **population-based data on 645 patients with metastatic RCC treated with TARGETED THERAPY.**[147] **A KPS < 80%, a diagnosis of RCC to systemic treatment interval < 1 year, anemia, hypercalcemia, neutrophilia, and thrombocytosis were all independent predictors for overall survival**
  - Patients in the favorable-risk group have zero factors with a median OS that was not reached (44 months in the external validation cohort),[186] intermediate-risk group have one or two risk factors (median OS, 27 months), poor-risk group have three or more risk factors (median OS, 8 months).
  - The IMDC model has also been shown to risk stratify patients previously treated with first line therapy.[187]

6.2 Rationale for Targeted and Immunotherapeutic Agents in Metastatic RCC

- An improved understanding of the molecular biology underlying metastatic RCC has led to the development of targeted agents to treat this disease.
- **Vascular endothelial growth factor (VEGF) overexpression in RCC is a result of inactivation of the VHL tumor suppressor gene**, which occurs in the majority of clear cell RCC cases. **Insufficient or inactive VHL leads to constitutive activation of HIF** and **over-production of HIF-related proteins, including VEGF. VEGF overexpression drives angiogenesis in RCC**.
  - Strategies to target the VEGF pathway include small molecule tyrosine kinase inhibitors (**sunitinib, sorafenib, pazopanib, cabozantinib tivozanib, and lenvatinib and axitinib**) that target VEGFRs and anti-VEGF directed antibodies (**bevacizuma**
- **Activation of the PI3K/Akt pathway, and in turn the mTOR** kinase, is another important pathway in RCC. mTOR is an important mediator of **tumor growth and proliferation, cellular metabolism, and is also an upstream activator of HIF-1. Activated mTOR results in the production of both VEGF and HIF-1**.
  - **Temsirolimus** and **everolimus** are mTOR kinase inhibitors.
- In addition to the above targeted agents, a number of **immune checkpoint inhibitors** have now been approved for the treatment mRCC, as monotherapy, or in combination with other checkpoint inhibitors or VEGF inhibitors:
  - **Nivolumab and pembrolizumab are anti-Programmed Death (PD)-1 monoclonal antibodies**. They act as an immunomodulator by blocking ligand activation of the PD-1 receptor on activated T cells.
  - **Avelumab is an anti-programmed death-ligand 1 (PD-L1) monoclonal antibody** that blocks the interaction of the PD-1 receptor with the PD-L1 ligand by directly targeting PD-L1 on tumor cells.
  - **Ipilimumab** is a monoclonal antibody that stimulates antitumor immunity by **blocking the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) receptor on T cells**.
  - The combination of **nivolumab with ipilimumab** is approved for the first-line treatment of mRCC and can produce durable responses but with increased risk of toxicity compared with either agent alone.
  - The following combinations are FDA- approved for the first-line treatment of RCC: the targeted agent **axitinib with either pembrolizumab or avelumab, nivolumab and cabozantinib, ipilimumab and nivolumab, and lenvatinib and pembrolizumab**
- **Targeted agents alone can produce durable partial responses and prolonged progression-free survival, but only very rarely can they produce durable complete responses.**
- The **immunotherapy agent IL-2** is a systemic treatment that is **capable of long-term remissions in a small fraction of well-selected patients with metastatic RCC**. Data from clinical trials have demonstrated a **6.7% complete response rate and 60% of patients with a complete response never experience disease recurrence**. However, IL-2 is has not been widely used because of **major toxicities and treatment-associated morbidity**, including capillary-leak syndrome and barriers associated with a requirement to administer the treatment as an inpatient.
- **Immune checkpoint inhibitors can also produce complete responses at rates similar to or higher than IL-2, often with low toxicity**

6.3 Targeted and Immune Checkpoint Therapies in the First-line Setting

- **Immune checkpoint inhibitors and VEGF-targeted therapies have improved patient outcomes and represent the mainstay of treatment for first-line advanced untreated mRCC.**
- Several approved targeted agents have shown efficacy in randomized, controlled, phase III trials as first-line treatment (**Table 11**).
  - **Sunitinib, bevacizumab plus interferon alpha (IFN-α), and temsirolimus** were compared with IFN-α in various studies.[188,189,190,191] Each was found to be **superior to IFN-α in prolonging progression-free survival** (PFS), per primary endpoint in the pivotal trials.
  - **Pazopanib** was shown to have **superior efficacy to that of placebo** in a phase III trial that treated approximately one half treatment naive patients and one half cytokine pretreated patients with a **PFS endpoint**.[192] A phase III randomized trial compared the efficacy and safety of pazopanib and sunitinib as first-line therapy. **Pazopanib and sunitinib demonstrated similar efficacy (in a non-inferiority trial), but the safety and quality-of-life aspects favoring pazopanib (COMPARZ trial).**[193] In addition, a randomized trial (**PISCES**), with the primary endpoint of **patient preference for a specific treatment**, randomized patients to receive either pazopanib or sunitinib. It showed that **patients preferred pazopanib (70%) over sunitinib (22%), with better quality of life profile for pazopanib**.
  - The majority of the patients in the sunitinib, bevacizumab plus IFN-α, and pazopanib trials were in the favorable or intermediate MSKCC risk groups. The majority of the patients in the temsirolimus study were in the poor MSKCC risk group.
  - The combination of **nivolumab with ipilimumab was compared with single-agent sunitinib** and was found to produce **higher objective response rates, complete response rates, as well as longer PFS and overall survival**.[194] The primary analysis of the trial focused on patients with **intermediate and poor risk mRCC** by IMDC prognostic criteria. Exploratory analyses of **favorable risk** patients suggested that the benefit of nivolumab/ipilimumab compared with sunitinib was less pronounced in this risk group.
  - The combination[195] of **pembrolizumab with the anti-VEGF tyrosine kinase inhibitor axitinib** was compared with sunitinib and shown to produce **higher objective responses, longer PFS, and longer overall survival** across all IMDC risk groups.
  - In addition, the combination **of avelumab with axitinib**[196] was compared with **sunitinib** and shown to produce **higher objective responses and longer PFS** (first independent primary endpoint) across all IMDC groups but has **not currently shown an overall survival benefit** (second independent primary endpoint).
  - [197] The combination of **cabozantinib with nivolumab** was compared to sunitinib and shown to produce **higher objective responses, longer PFS, longer overall survival** and **better health-related quality of life** across all IMDC groups.
  - Subsequently,[198] the combination of **lenvatinib with pembrolizumab** was compared to sunitinib and found to produce **highe objective responses, longer PFS**, and **longer overall survival** across all IMDC groups. The complete response rate of 16.1% (57/355 patients) observed with lenvatinib plus pembrolizumab was particularly notable.
  - In current practice, patients with treatment-naïve:
    - **Patients with good risk clear cell mRCC are recommended to receive a VEGF-inhibitor and checkpoint inhibitor combination or VEGF-inhibitor alone** . Active surveillance is appropriate in selected cases based on prospective phase 2 data[199] showing that a subset of patients with mRCC can safely undergo surveillance prior to starting systemic therapy.
    - **Patients with intermediate or poor risk disease** are recommended to receive **nivolumab+ipilimumab** or a **combination of immune checkpoint therapy with a tyrosine kinase inhibitor (TKI) such as:**
      - **Pembrolizumab or avelumab plus axitinib**
      - **Nivolumab plus cabozantinib**
      - **Pembrolizumab plus lenvatinib**
  - The most commonly reported **adverse events for targeted therapies** in clinical trials for RCC can be divided by medication:
    - **VEGF/TKI**: diarrhea, nausea, hypertension, hypothyroidism, proteinuria, myelosuppression, mucositis, diarrhea hand-foot-skin reaction, GI symptoms.
    - **Bevacizumab + IFN-alpha**: constipation, stomatitis, dry skin, hypertension, fatigue, mucosal inflammation, neutropenia anorexia.
    - **Temsirolimus**: constipation, diarrhea, stomatitis, acneiform rash, pruritus, cough/dyspnea, epistaxis, fatigue, mucosal inflammation, hyperglycemia, thrombocytopenia, elevated liver enzymes, bacterial infections.
    - **Everolimus**: diarrhea, stomatitis, dry skin, pruritus, bacterial infections, cough/dyspnea, mucosal inflammation, proteinuria, elevated liver enzymes, neutropenia, thrombocytopenia.
    - **Immune checkpoint inhibitors** (nivolumab, ipilimumab, pembrolizumab, avelumab): mediated by host immune response and include dermatitis, colitis, pneumonitis, hypophysitis, endocrinopathies, fatigue and non-specific fevers.
  - **Non-clear cell RCC:** All treatments for mRCC have been validated mainly for **clear cell renal cell carcinoma tumors**. The

efficacy of these regimens both in the first line and second line settings can substantially differ in **non-clear cell renal cell carcinoma histologies**. Several clinical trials have been completed or are underway to develop therapies specific to non-clear cell tumors.[200]

- **SWOG 1500 (PAPMET)**[201]
  - Prospective, randomized, open-label, phase 2 trial of 152 patients with advanced papillary RCC randomized to cabozantinib, sunitinib, crizotinib or savolitinib.
  - **Assignment to crizotinib and savolitinib was stopped early due to futility** at a preplanned interim analysis. **PFS was longer in cabozantinib group (9.0 vs 5.6 months)**

Table 11. Randomized Phase III Trials of Targeted Agents for First- and Second-Line Treatment of Metastatic Renal Cell Carcinoma

Study	n	MSKCC Risk Group[t]	ORR %	Median PFS, months	Final Median OS, months
Sunitinib vs. IFN-α[188]	750	Good/Intermediate	47 vs 12	11 vs 5 *P* < 0.001	26.4 vs 21.8 *P* = 0.051
Bevacizumab plus IFN-α vs. IFN-α[191]	649	Good/Intermediate	31 vs 12	10.4 vs 5.5 *P* < 0.0001	23.3 vs 21.3 *P* = 0.1291
Bevacizumab plus IFN-α vs. IFN-α[190]	732	Good/Intermediate	25.5 vs 13.1	8.4 vs 4.9 *P* < 0.0001	18.3 vs 17.4 *P* = 0.069
Pazopanib vs. placebo[202]	233	Good/Intermediate	30 vs 3*	11.1 vs 2.8 *P* < 0.000001	N/A
Temsirolimus vs. IFN-α[189]	626	Poor	8.6 vs 4.8	5.5 vs 3.1 *P* < 0.001	10.9 vs 7.3 *P* = 0.069
Pazopanib vs. Sunitinib[203]	1110	Good/Intermediate	31 vs 25	8.4 vs 9.5 HR = 1.466	28.4 vs 29.3 *P* = 0.275
Everolimus vs. placebo[204]	416	Good/Intermediate	2 vs 0	4.9 vs 1.9 *P* < 0.001	14.8 vs 14.4 *P* = 0.162
Axitinib vs. Sorafenib[205]	723	Good/intermediate[†]	23 vs 12	8.3 vs 5.7 *P* < 0.0001	20.1 vs 19.2 *P* = 0.3744
Nivolumab vs. Everolimus[206]	821	All	25 vs 5	4.6 vs 4.4 *P=0.11*	25 vs 19.6
Cabozantinib vs. Everolimus[207]	658	All	17 vs 3	7.4 vs 3.9 *P<0.0001*	24.1 vs 16.5 *P=0.00026*
Lenvatinib+Everolimus vs. Lenvatinib versus Everolimus (phase II)[208]	153	All	43 vs 27 vs 6	14.6 vs 7.4 vs 5.5	25.5 vs 19.1 vs 15.4
Cabozantinib vs. Sunitinib (phase II)[209]	157	Intermediate/Poor (IMDC)	20 vs 9	8.6 vs 5.3 P=0.0008	26.6 vs 21.2

Nivolumab+Ipilimumab vs. Sunitinib[192-194]	1096	All (but primary analysis only on intermediate/poor IMDC)	42 vs 29	8.2 vs 8.3 HR=0.77, P=0.0014	Not reached vs 26.6 P<0.001
Pembrolizumab+Axitinib vs. Sunitinib[195]	861	All (IMDC)	59 vs 35.7	15.1 vs 11.1 HR=0.69 P=0.0001	Not yet reached in either group but OS at 18 months was 82.3% vs 72.1% P<0.0001
Avelumab + Axitinib vs. Sunitinib[196]	886	All (IMDC)	51.4 vs 25.7	13.8 vs 8.4 HR=0.69 P<0.001	N/A
Nivolumab + cabozantinib vs. sunitinib[197]	651	All (IMDC)	55.7 vs 27.1	16.6 vs 8.3 HR 0.51 P<0.001	Not yet reached in either group but OS at 12 months was 85.7% vs 75.6% HR=0.60 P=0.001
Pembrolizumab + lenvatinib vs. lenvatinib + everolimus vs. sunitinib[197]	1069	All (IMDC)	71 vs 53.5 vs 36.1	23.9 vs 14.2 vs 9.2 HR 0.39 and P<0.001 for pembrolizumab + lenvatinib vs sunitinib HR 0.65 and P<0.001 for lenvatinib + everolimus vs sunitinib	Median OS was not reached with any of the three treatment regimens HR 0.66 and P=0.005 for pembrolizumab + lenvatinib vs sunitinib HR 1.15 and P=0.30 for lenvatinib + everolimus vs sunitinib

IFN-α - interferon alfa;
ORR - objective response rate;
PFS - progression-free survival;
OS - overall survival;
HR - hazard ratio

t - Predominant MSKCC Risk Group
* - Treatment-naïve or cytokine-refractory mRCC
† - Predominant IMDC Risk Group[210]

6.4 Targeted Therapies in the Second line Setting and Beyond

- Even in the era of immunotherapy and targeted agents, **most patients with metastatic RCC experience disease relapse**. Following failure of first-line treatment for metastatic RCC, treatment recommendations for patients with relapsed or recurrent disease are primarily limited to **targeted agents and immune checkpoint therapy**.
- **Everolimus** is approved for the treatment of advanced RCC **following treatment failure with sunitinib and sorafenib**.
  - A multi-center, double-blind randomized phase III trial compared everolimus with placebo in 416 patients with progressive advanced RCC **following sorafenib or sunitinib** treatment.[204,211] **Median PFS was significantly prolonged in patients treated with everolimus compared with placebo**.
- The combination of **everolimus** with the anti-VEGF tyrosine kinase inhibitor **lenvatinib** has been approved **for patients with mRCC who have progressive disease following at least one prior VEGF-targeted therapy**.
  - Regulatory approval of the combination of lenvatinib + everolimus was based on a randomized, phase 2, open-label, multicenter trial which showed that the combination of **lenvatinib + everolimus produced more objective responses and prolonged progression-free survival compared with everolimus alone**.[208]
- **Axitinib** was approved based on results from the Axitinib versus Sorafenib (AXIS) trial, a global, randomized phase III trial comparing axitinib with sorafenib as second-line therapy in 723 patients with treatment-refractory RCC.[205,212] **Median PFS was significantly longer in patients treated with axitinib versus sorafenib**.
- **Nivolumab** was approved on the basis of the CheckMate 025 trial which compared everolimus to nivolumab in previously treated patients (one or two lines of antiangiogenic therapy).[206] **Median OS for Nivolumab was 25 months vs 19.6 months for Everolimu**
- **Cabozantinib**, an oral, small-molecule tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR) as well as MET and AXL was compared to everolimus in patients who had progressed on prior anti-VEGFR therapy –METEOR trial.[207] **Median progression-free survival was 7.4 months with cabozantinib and 3.9 months with everolimus, with median OS in patients treated with cabozantinib reaching 24.1 months, as compared to 16.5 months with everolimus**.
- **Tivozanib** is an oral VEGF-targeted tyrosine kinase inhibitor that has been FDA approved for relapsed or refractory advanced RC following ≥2 prior systemic therapies. This was based on the TIVO-3 trial which compared tivozanib to sorafenib. **Median progression-free survival was 5.6 months with tivozanib and 3.9 months with sorafenib (Hazard ratio 0.73, p=0.016)**. However, the OS results were inconclusive with a median OS in patients treated with tivozanib of 16.4 months, as compared to 19.2 months with sorafenib (**stratified HR 0.97 with 95% confidence intervals of 0.75 to 1.24**).
- Treatment paradigms for advanced kidney cancer are classified by line of therapy, risk score and level of evidence (**Table 12**).

Table 12. Treatment Algorithm for Patients with Metastatic clear cell RCC

Treatment Options*		
Patient Group	**Level 1‡**	**≥ Level 2‡**
Patient Group	**Level 1‡**	**≥ Level 2‡**
Treatment Naive		
Favorable risk	Pembrolizumab + Axitinib Avelumab + Axitinib Nivolumab + Cabozantinib Pembrolizumab + Lenvatinib Sunitinib Pazopanib Bevacizumab + IFN	Nivolumab+Ipilimumab Cabozantinib Axitinib High-dose IL-2 Sorafenib
Intermediate/Poor risk	Nivolumab+Ipilimumab Pembrolizumab+Axitinib Avelumab + Axitinib Nivolumab + Cabozantinib Pembrolizumab + Lenvatinib Temsirolimus (poor risk patients) Sunitinib Pazopanib	Cabozantinib Axitinib High-dose IL-2
Previously treated		
Preferred regimens	Nivolumab Cabozantinib	Lenvatinib + everolimus
Other recommended regimens	Axitinib Tivozanib	Pembrolizumab + axitinib Avelumab + axitinib Cabozantinib+nivolumab Ipilimumab+ nivolumab Pembrolizumab+ lenvatinib Pazopanib Sunitinib
Useful under certain circumstances		Bevacizumab Sorafenib Everolimus High dose IL-2 for selected patients with excellent performance status and normal organ function

		Temsirolimus Belzutifan

*Adapted from AM Molina, 2008, with permission.[214]

‡Levels described at www.nccn.org/professionals/physician_gls/categories_of_consensus.asp

6.5 Role of Radical Nephrectomy in the Setting of Metastatic Disease

- **Two clinical trials** published in 2001[215,216] conducted in the United States and Europe have demonstrated a **survival benefit for patients with metastatic disease treated with cytoreductive nephrectomy and cytokine therapy (Interferon-alpha) compare to cytokine therapy alone**. In these studies, results showed an **overall survival advantage of approximately 6 months benefiting patients treated with cytoreductive nephrectomy**.
  - Large retrospective analyses from the IMDC cohort have shown similar benefit in patients with 3 or less risk factors undergoing cytoreductive nephrectomy.[147] Similar results favoring surgery were shown retrospectively in a large population-based study using the NCDB database.[217]
- Two phase III randomized clinical trials conducted to study the role of cytoreductive nephrectomy in patients treated with sunitinib were completed.
  - **SURTIME**[218] (**upfront cytoreductive nephrectomy + sunitinib versus sunitinib then cytoreductive nephrectomy then sunitinib**) was stopped early due to poor accrual. **Deferred CN did not improve the 28-week progression-free recurrenc** However, with the deferred approach, more patients received sunitinib and OS results appeared to be higher. As such, presurgical sunitinib may identify patients with inherent resistance to systemic therapy before CN. Given that only **99/458 planned patients were accrued**, these post-hoc analyses remain largely exploratory. The study was also limited by **ineligibility** given that 18% of patients received off-protocol treatment.
  - **CARMENA** (**a non-inferiority randomized phase III study comparing cytoreductive nephrectomy then sunitinib versus sunitinib only**)[186] included 450 patients with clear cell RCC (45% MSKCC intermediate-risk, and 55% MSKCC poor-risk). The study concluded that **sunitinib alone was not inferior to cytoreductive nephrectomy followed by sunitinib**. Limitations o CARMENA include **early closure for poor accrual** (450/576 planned over 8 years), **enrichment with poor risk disease**, off-protocol therapy (**cross-over, noncompliance**, etc.) in > 50% of both arms which may represent an inherent bias for the surgical approach. However, the results of this study have underscored that **cytoreductive nephrectomy should not be considered as first line therapy universally in mRCC**, especially in intermediate and poor risk disease.
    - **Patient selection** is critical when deciding whether or not proceed with cytoreductive nephrectomy. Clinical characteristics that are associated with better outcomes include, good performance status, absence of brain, liver or extensive bone metastases, clear cell histology with the absence of sarcomatoid differentiation, and the ability to debulk the majority of the tumor burden with surgery.
- Patients should be counseled of the possibility that surgical complications or rapid postoperative disease progression (< 5% of patients) with upfront cytoreductive nephrectomy could preclude them from receiving systemic therapy.

6.6 Local Treatment for Metastatic RCC Tumors

- Long term survival following complete surgical removal (primary and metastatic RCC sites) without systemic therapy is reported in rare cases of many historical series.[219]
- Local treatments for mRCC include surgery, radiation therapy, and percutaneous image-guided ablative techniques such as therm ablation, cryoablation, and microwave ablation.
- Surgical metastasectomy is increasingly used for mRCC, although the data regarding its efficacy and safety are predominantly retrospective.[220,221]
  - Retrospective evidence suggests that complete metastasectomy, when feasible, is associated with better outcomes than incomplete metastasectomy.[221]
- Radiation therapy for metastatic disease can be divided into 1) **palliative radiotherapy** intended to alleviate symptoms from a metastatic lesion and 2) **definitive radiotherapy** intended to fully eradicate and provide long-term local control of a metastatic lesi
- Historically, the efficacy of palliative radiotherapy in mRCC has been well-established in prospective studies,[222] whereas definitive radiotherapy is less commonly utilized. However, improvements in radiation therapy delivery using approaches such as stereotacti body radiotherapy are now motivating the prospective investigation of definitive radiotherapy.[223]
  - A single-arm, single-center phase II feasibility trial of definitive radiotherapy in lieu of systemic therapy in 30 patients with oligometastatic mRCC suggested that definitive radiotherapy can facilitate deferral of systemic therapy initiation and allow sustained systemic therapy breaks for select patients with oligometastatic mRCC.[224] The median progression-free survival (PFS was 22.7 months with 1-year PFS probability of 64%.
  - Oligometastatic mRCC is typically defined as having five or fewer metastatic lesions.
- Definitive radiotherapy is also being explored for the treatment of oligoprogressive lesions in mRCC, with the goal to delay the nee to change systemic therapy.
  - A multicenter single-arm phase II trial in 37 patients found that definitive radiotherapy can delay the need to change systemic therapy for a median of > 1 year.[225]
  - A single-center single-arm phase II trial in 20 patients found that definitive radiotherapy delayed the need to change systemic

therapy for a median of 11.1 months without significant decline in quality of life.[226]

- Definitive radiotherapy is also being prospectively explored in combination with immunotherapy agents in patients with oligometastatic mRCC. It remains, however, to be determined whether the addition of immunotherapy is beneficial over radiotherapy alone.
  - RAPPORT was a single-arm, multi-institutional phase I/II trial that tested the safety and efficacy of stereotactic body radiotherapy administered to all metastatic lesions in combination with short-course pembrolizumab in 30 patients with oligometastatic mRCC. The 1-year and 2-year PFS probabilities were found to be 60% and 45%, respectively.[227]
- Percutaneous image-guided ablation procedures are currently less studied in mRCC than either metastasectomy or radiation therapy. Retrospective studies suggest that such approaches are safe and can achieve reasonable local control in mRCC.[228,229]
- Local treatment of metastatic sites is most appropriate for patients **with solitary or oligometastatic RCC that is either surgically resectable or amenable to definitive radiotherapy or ablation procedures**.
  - There are no high-quality data comparing metastasectomy to definitive radiation therapy or ablation procedures in mRCC. Each can be considered on case-by-case basis based on anatomic location, patient co-morbidities, recovery times and anesthesia needs (radiation therapy and ablation procedures do not require general anesthesia).[221]
  - An additional consideration is that radiation therapy can typically be safely administered for all oligometastatic mRCC lesions whereas complete metastasectomy may be too invasive and less feasible in some cases.
- No randomized clinical trials have been performed to demonstrate the absolute benefits of metastasectomy or radiation therapy to oligometastatic sites alone or in combination with systemic therapies. However, there is a strong rationale for treatment of patients when local treatment can delay the cost and adverse effects associated with systemic mRCC therapies.

7. AUA Guideline Webcast

AUA Guidelines 2017: Renal Cell Cancer

Videos

Robotic partial nephrectomy for multiple renal tumors

Robotic partial nephrectomy for hilar tumors: zero ischemia or early unclamping?

Retroperitoneal robotic partial nephrectomy: a step-by-step guide

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ROBOTIC PARTIAL NEPHRECTOMY WITH SELECTIVE SEGMENTAL ARTERIAL CLAMPING

Enucleation techniques for challenging robot-assisted partial nephrectomy cases

Robotic-assisted Laparoscopic Partial Nephrectomy for a Complex Cystic Tumor: Tips, Tricks, and Troubleshooting

3D LAPAROSCOPIC PARTIAL NEPHRECTOMY FOR COMPLEX RENAL MASS

TECHNIQUES FOR ROBOTIC NEPHRECTOMY WITH VENA CAVAL TUMOR THROMBECTOMY

V-LOCK FOR HEMOSTASIS AND RECONSTRUCTION IN MINIMALLY ACCESS PARTIAL NEPHRECTOMY.

Left laparoscopic radical nephrectomy: Step-by-step

Right laparoscopic radical nephrectomy: Step-by-step

Totally Laparoscopic Radical Nephrectomy with Thrombectomy Level IV

Laparoscopic Radical Nephrectomy

V01-01: Robotic-assisted Partial Nephrectomy: Tips and Tricks for Challenging Scenarios

CT Guided Percutaneous Radiofrequency Ablation of Renal

Presentations

Renal Neoplasms Presentation 1

Renal Neoplasms Presentation 2

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