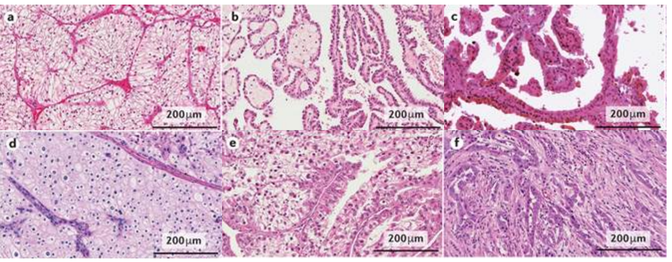
How I think about: Renal Cell Carcinoma

What is RCC?

- Cancer originating from the kidney.
- 75000 new cases in US yearly and 15000 yearly deaths
- Male to Female ratio = 2:1
- Median age at diagnosis = 64 years
- Histologies: Clear cell RCC (80% of all RCC) versus non-clear cell RCC (20%)



(Hsieh et al., Nat Rev Dis Primers, 2017)

a) Clear cell RCC (ccRCC); b) Papillary RCCs type 1 (basophilic); c) Papillary RCC type 2 (eosinophilic); d) Chromophobe RCCs; e) MiT family translocation RCCs and f) collecting duct RCCs.

How do patients present?

- Incidental
- Local symptoms (Hematuria most common finding, flank pain).
- Systemic symptoms (Fever, weight loss, night sweats; paraneoplastic syndromes)
- Classic triad (flank pain, hematuria, and a palpable abdominal mass): 9% of patients

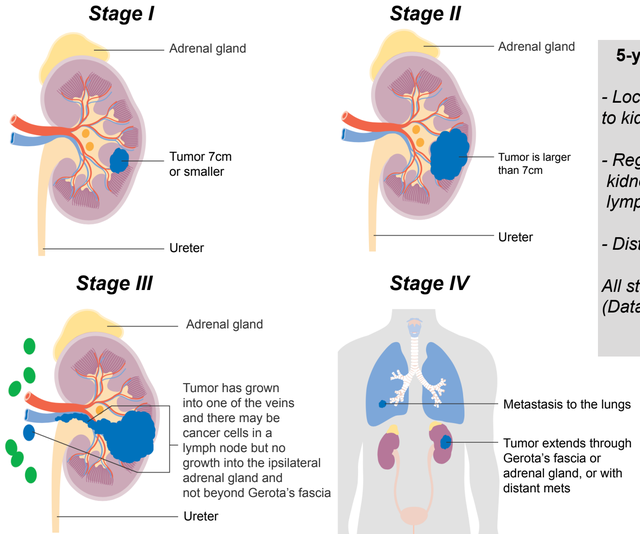
Initial workup

H&P	Labs	Imaging	Tissue Diagnosis
Local symptoms: pain, hematuria	CBC	Abdominal (+pelvic) imaging (CT with IV contrast or MRI)	Biopsy standard for advanced disease (cytoreductive nephrectomy considered in some circumstances)
Systemic symptoms: Fever, weight loss, night sweats; paraneoplastic syndromes	BMP & LFTs	Chest imaging (CXR technically OK for small, localized disease, but prefer CT chest)	For localized renal mass with high degree of suspicion, biopsy is sometimes not performed prior to nephrectomy
	UA	Guided by symptoms: MRI brain, bone scan	
	LDH		

Pearls

- Bilateral RCCs suggest a possible genetic cancer predisposition syndrome
- Stauffer's syndrome: Paraneoplastic syndrome of hepatic dysfunction in the abscence of liver metastasis.

Staging and 5-year survival



(Adapted from Wikimedia)

5-year overall survival

- Localized (spread restricted to kidney) - OS 93%

- Regional (spread outside the kidney to nearby structures or lymph nodes) - OS 70%

- Distant (stage IV) - 13%

All stages combined: 75% (Data obtained from SEER)

Principles of treatment:

Very Early (T1a)	Early (Stage I/II)	Locally advanced (Stage III)	Advanced (Stage IV)
Partial nephrectomy	Nephrectomy	Nephrectomy	Systemic therapy
Ablation is alternative (but should obtain tissue diagnosis first!)		Adjuvant therapy is conterversial (sunitinib FDA approved; but conflicting data, and no OS benefit)	Consider cytoreductive nephrectomy in specific circumstances
Active surveillance for some patients with small renal masses (SRMs)			

Risk Stratification for advanced disease: IMDC vs MSKCC

RISK FACTOR	MSKCC RISK FACTORS	IMDC RISK FACTORS
Time from diagnosis to systemic treatment < 1 year	X	X
Hemoglobin less than lower limit of normal	X	X
Calcium greater than upper limit of normal	X	X
Performance Status (Karnofsky) <80%	X	X
LDH greater than 1.5 upper limit of normal	X	
Neutrophil count greater than upper limit of normal		X
Platelet count greater than upper limit of normal		X

(Adapted from urotoday)

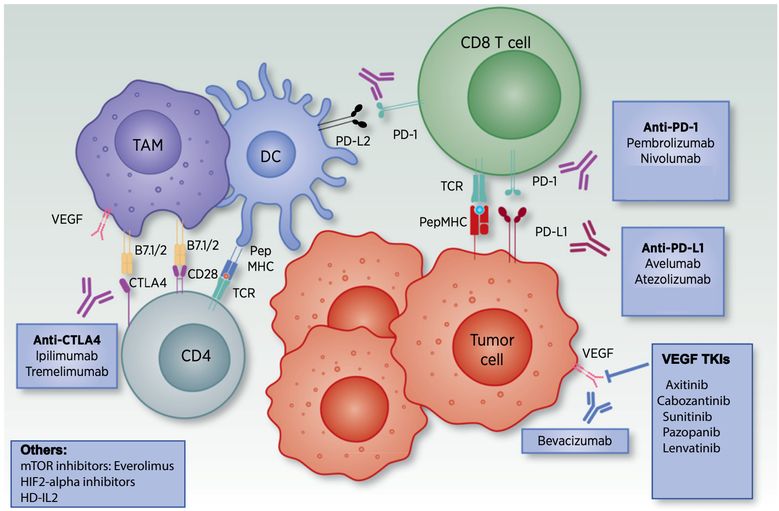
0 Risk factors = Favorable prognosis, 1-2 Risk Factors = Intermediate, >2 Risk Factors = Poor
Note: Patients with de novo metastatic disease are at least intermediate risk

What is systemic therapy in advanced RCC?

First step: Calculate IMDC Risk score and categorize patients into favorable/intermediate/poor

1st line	2nd line and beyond*	Considerations
IMDC Favorable risk: Pembro+Axitinib VEGF monotherapy (Sunitinib, cabozantinib, pazopanib) acceptable here	VEGF TKI monotherapy: Cabo, axitinib>>>sunitinib, pazopanib	Cytoreduction for oligometastatic disease
IMDC Intermediate/poor risk: Combination therapy (Pembro+axitinib or Nivo/Ipi)	Lenvatinib + Everolimus	Radiation: RCC historically considered radioresistant, but newer data does indicate responsiveness to SBRT which is now an emerging treatment option
Rarely used (but approved in certain circumstances): VEGF monotherapy, HD-IL2, temsirolimus	Everolimus monotherapy	

*** Treatments on the horizon: HIF2-alpha inhibitors, Tivozanib**



(Aggen et al., Clin Cancer Res., 2020)

Figure: PD-1/PD-L1 targeted therapeutics in RCC. Overview of current immunotherapy targets in RCC. The PD-1 antibodies pembrolizumab and nivolumab prevent interaction with PD-L1 and PD-L2. In contrast, the PD-L1 antibodies avelumab and atezolizumab prevent PD1 ligation, but leave PD-1 and PD-L2 ligation unopposed.

"Deep Dive" questions:

- Is there a role for cytoreductive nephrectomy in metastatic RCC patients?
- Is there a role for adjuvant therapy in RCC treatment?
- When do you consider surgical resection in metastatic disease?
- How do you treat patients who progressed on immune checkpoint inhibitor therapy?

References
1. Aggen DH, Drake CG, Rini BI. Targeting PD-1 or PD-L1 in Metastatic Kidney Cancer: Combination Therapy in the First-Line Setting. Clin Cancer Res. 2020;26(9):2087-95.
2. Hsieh JJ, Purdue MP, Signoretti S, Swanton C, Albiges L, Schmidinger M, et al. Renal cell carcinoma. Nat Rev Dis Primers. 2017;3:17009.
3. Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019;380(12):1116-27

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