Bladder Cancer

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Speaker Background – Surgeon/Scientist

- **Surgery patients with cancers of the bladder, kidney, and prostate**
  - Open radical cystectomy
  - Robotic radical cystectomy
  - Open radical nephrectomy
  - Robotic partial nephrectomy
  - Robotic radical prostatectomy
- **Immunotherapy laboratory researcher**
  - Bladder cancer

Background and Contact Information

- MD: **Northwestern**
- Urology residency: **Johns Hopkins**
- Urologic Oncology fellowship: **MD Anderson Cancer Center**

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Disclosures

Department of Defense Career Development Award

Naren Patel Genitourinary Research Fund

The Ohio State University Comprehensive Cancer Center
Laboratory Startup

Consulting/Honoraria:
Research Square
Janssen
Arquer
SurvivorNet

How are we increasing our knowledge of how immune cells interact with bladder cancers?

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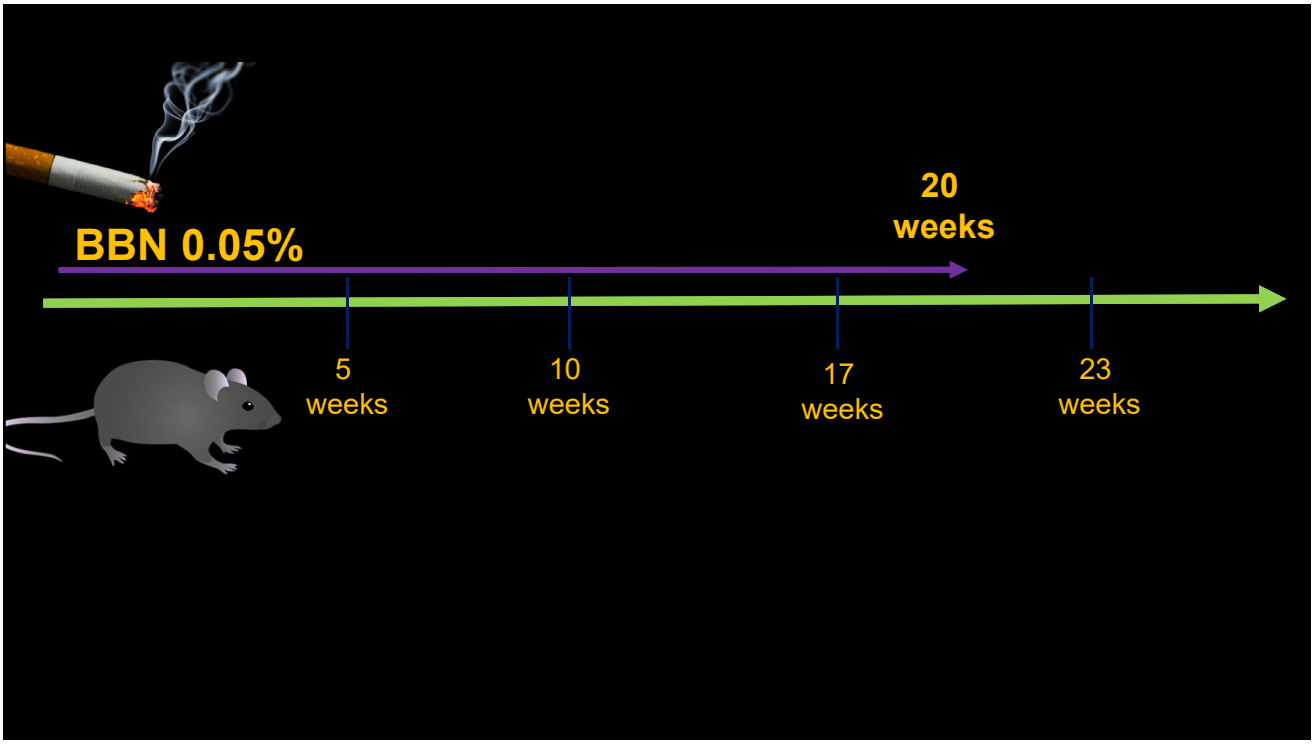
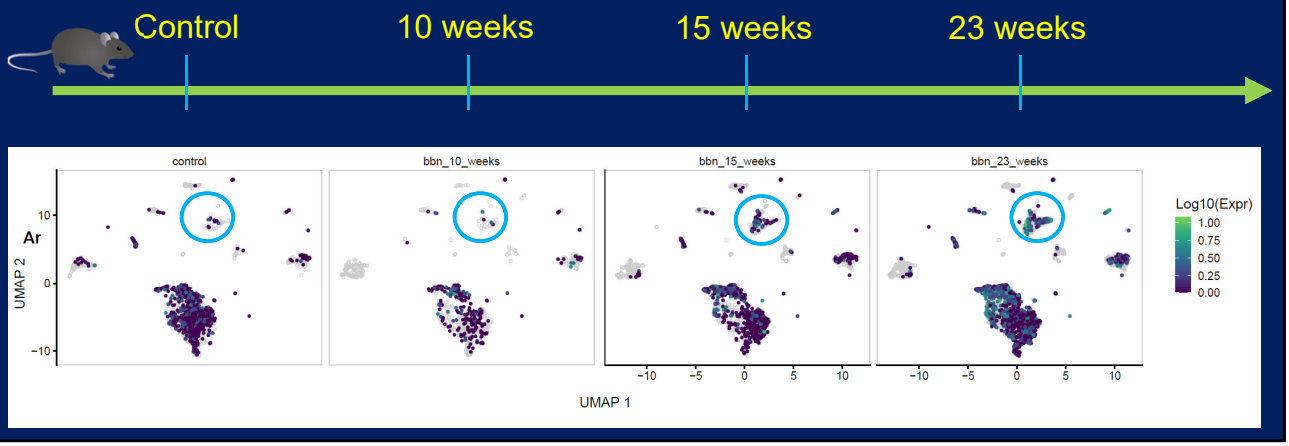


Urology

Androgen Receptor in T cells



Bladder Cancer: Broad Glance

80,000 incident cases/yr (U.S.)
6th most common cancer type
4:1 male:female incidence
5th most common cancer in males
The most $$$ cancer to treat per patient per lifetime
Smoking is the #1 environmental risk factor

#1 Warning sign: Hematuria

Gross hematuria: immediately refer to urology for flexible cystoscopy; order CT Urogram – this will completely evaluate the lower (bladder) and upper urinary tracts (ureters, renal pelvises)

Microhematuria: what to do? It depends. Fortunately robust guidelines exist (AUA/SUFU)

Intermediate risk:
11-25 RBC/HPF or
10-30 pack years or
Women 50+; Men 40+

Cysto + renal US

High risk:
>25 RBC/HPF or
Hx of gross hematuria or
>30 pack years or
Women 60+; Men 60+

Cysto + CT urogram

Microhematuria:
3 or more RBC per HPF
If symptoms of UTI, culture and treat
Consider risk factors:
Anyone at intermediate or high risk needs a cystoscopy

Case

- In January 2019, a 62 year old man was referred to the urologic oncology clinic because he was diagnosed with cT1 HG urothelial carcinoma of the bladder

- **What does that mean?**
- **What do we need to do?**

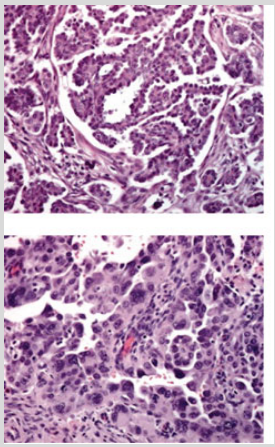
Tumor stage

- T1-4 can be based on size and/or depth of invasion

T stage:	T1	T2	T3	T4
Bladder cancer (based on depth of invasion)	Involves only the urothelium (epithelial cell layer lining the bladder or the underlying 'lamina propria'	Invades muscular backing of bladder (muscularis propria)	Invades fatty layer surrounding bladder (perivesical fat)	Invades other organs in pelvis (prostate, rectum, vagina, pelvic floor muscles)

Tumor grade

- Refers to how aggressive the cancer cells look (microscope)



← **Low** grade

← **High** grade

Bladder cancer N stage

- N0-3 clinical (radiographic) assessment of lymph nodes

N stage:	N0	N1	N2	T3
		1 cancer involved lymph node in true pelvis (**external iliac, internal iliac, obturator**)	Cancer involved lymph nodes in true pelvis (**external iliac, internal iliac, obturator**)	Cancer involved **common iliac** lymph node(s)

Bladder cancer M stage

- M0-1

M stage:	M0	M1a	M1b
		Distant lymph node(s) involved (**retroperitoneal**)	Visceral or bony mets

Is surgery on the table as a treatment option? Rules of thumb…

T1-3 N0 M0	T4 N0 M0	T any N1 M0	T any N0-1 M1
Yes	Maybe (consider adding chemo and/or radiation)	No*	No*

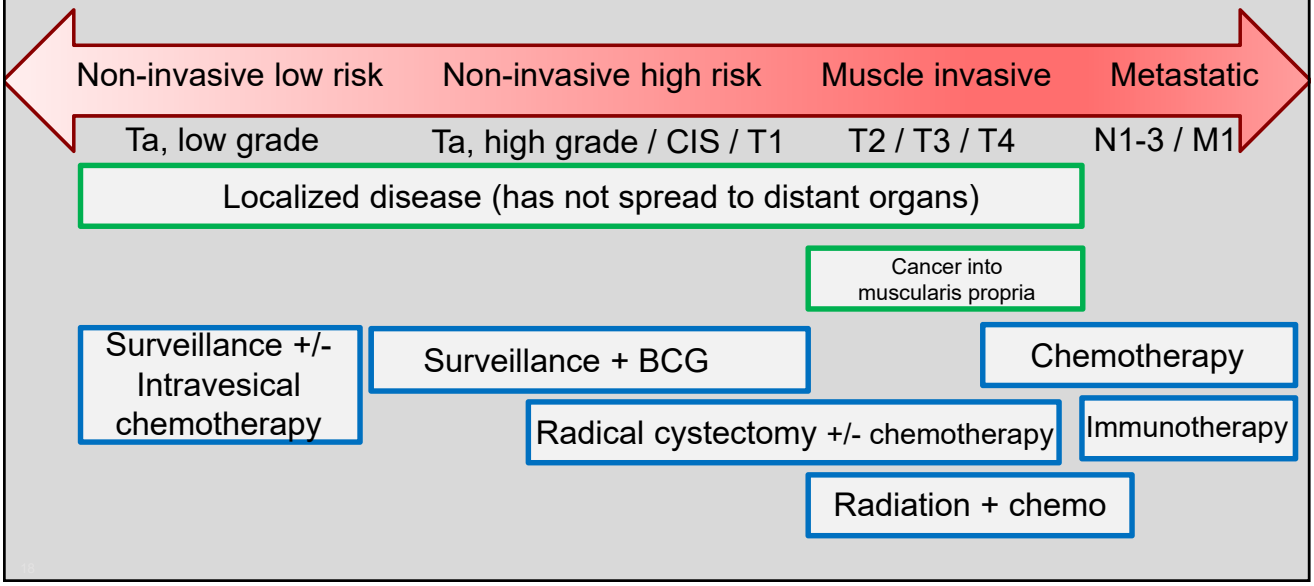
*Exceptions: Sometimes we do perform surgery in patients with metastatic cancers because

- Colorectal cancer
- Breast cancer
- Kidney cancer

Back to the case

- My patient. CT scans were performed. Based on negative scans, N0, M0. He is a surgical candidate.
- What does T1 HG urothelial carcinoma of the bladder mean?

Bladder Cancer treatment depends on grade & stage



What do we do, doc?

- What are the treatment options?

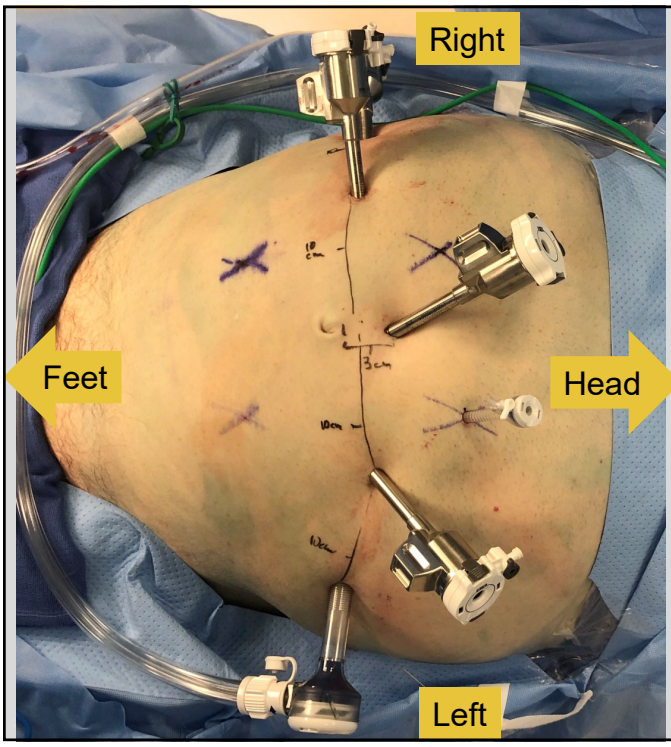
- 1. Nothing – come back in 3 months for cystoscopy
- 2. BCG – intravesical immunotherapy – once a week washes into the bladder of live bacteria that cause inflammation in the bladder
- 3. Radical surgery cystectomy – surgical removal of the bladder, 'wide surgical resection' (radical) that entails removal of regional lymph nodes, and sometimes, also of surrounding organs

What did my patient do?

1. Do nothing
2. BCG immunotherapy
3. Radical surgery (cystoprostatectomy with bilateral extended pelvic lymph node dissection and ileal conduit urinary diversion)

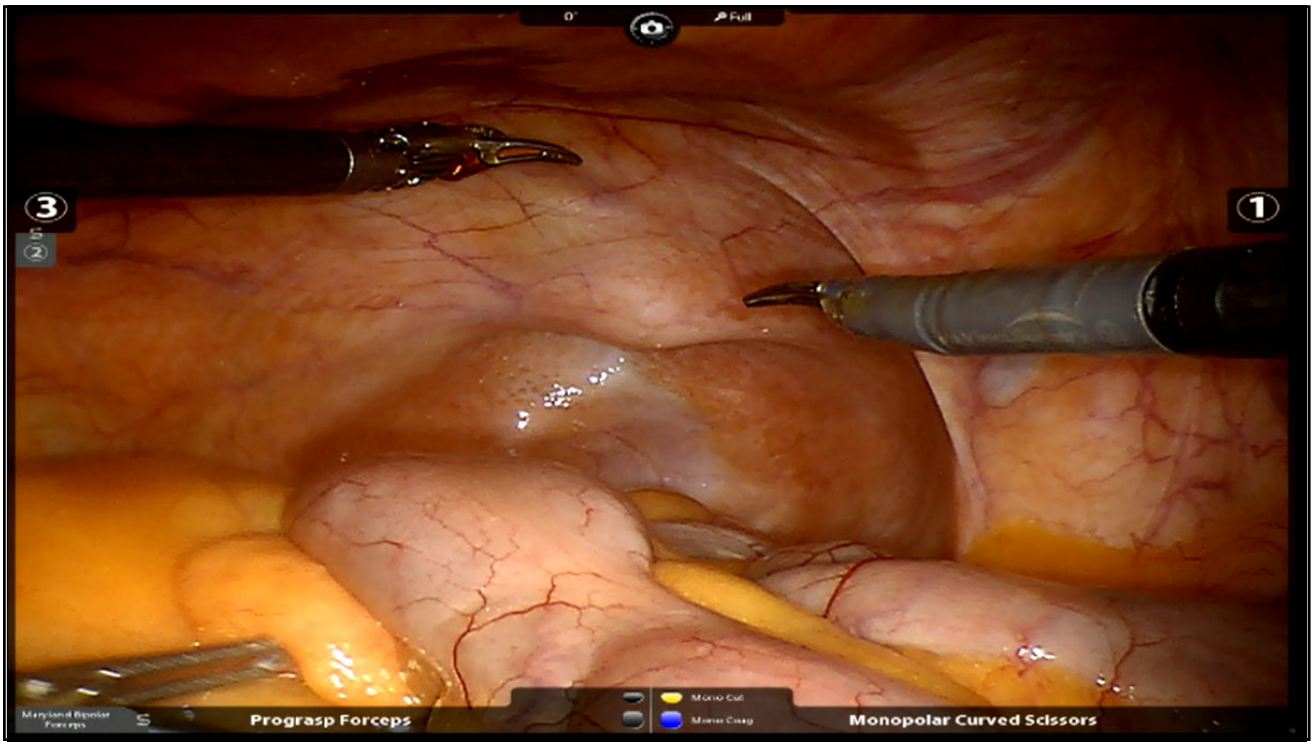
It's aggressive: 12-22% chance of death due to T1HG bladder cancer even after surgery (Kulkarni et al. *Eur Urol* 2010)

Being proactive could be good: cystectomy 1st associated with better survival compared to BCG 1st followed by surgery later if BCG didn't work (Herr, *J Urol* 2001)



Port Placement

Using Da Vinci Xi docked on patient right and assistant on patient left. Photo orientation: caudal is picture left, cranial is picture right, patient left is picture bottom. The left lateral most trocar is a 12mm AirSeal assistant port. The cranial most trocar in the left upper quadrant is a 5mm assistant port. All other trocars are Xi 5mm robotic trocars, spaced 10cm apart.



Concluding points

- Risk factors for bladder cancer include male sex and smoking
- Gross hematuria → cystoscopy with urology
- Microhematuria in a patient with intermediate or high risk features (AUA/SUFU guideline) → cystoscopy with urology
- Bladder cancer stage and grade determine optimal treatment options

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Kidney Cancer

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Kidney Cancer: Outline

- **Epidemiology/Clinical Presentation**
- **Renal Mass Evaluation:**
  - Imaging
  - Role for Biopsy
- **Localized Kidney Cancer Treatment**
  - Surveillance, Ablation, Surgery
- **Advanced/Metastatic disease**

Kidney Cancer

- Kidney Cancer =
- Renal Cancer =
- Renal Cell Carcinoma (RCC)

Kidney Cancer

Kidney Cancer 2022

- **Incidence**
  - 79,000 new cases
  - 13,920 deaths
- Peak incidence 5th-7th decades
- Men (50K) > Women (29K)
- Lifetime Probability of Developing Renal Cancer:
  - 1 in 46 male (#6)
  - 1 in 79 female (#9)

American Cancer Society. *Cancer Facts & Figures 2022.*

Risk Factors

- **Obesity**
  - May account for ~40% of cases in US
  - Risk increases ~30% for every 5kg/m^2 increase in BMI
- **Tobacco Exposure**
  - May account for ~20% of cases
- Hypertension
- Possible chemical links:
  - Trichloroethylene (TCE)
  - Perfluorooctanoic acid (PFOA or C8)

Clinical Presentation

- **80% incidental**

- **Flank pain**
- **Gross hematuria**
- **Palpable mass**

← **"Classic Triad" <10%**

- **Microhematuria**

- **Paraneoplastic syndromes (10-20%)**

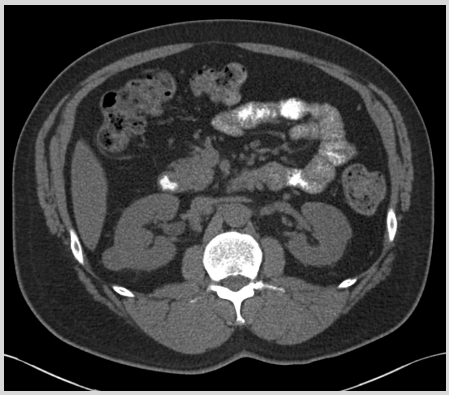
Renal Mass: Radiographic Assessment

- Ultrasound
- CT
- MRI

- Key Point:
  - Need to determine **enhancement**

CT Scan

- **Hounsfield Units** (HU)
  - Represents the **density of tissue**
  - Quantitative measurement



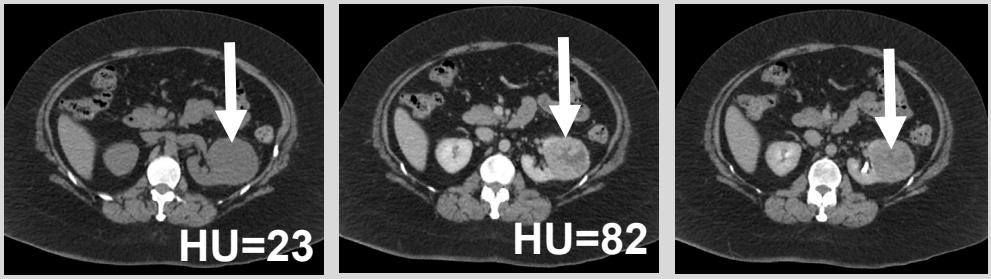
Tissue	HU
Bone	+1000
Blood	40
Kidney	30
Water	0
Fat	-50
Air	-1000

Enhancement

- Can only be determined if a contrast agent is used:
  - **CT**: Iodinated contrast
    - **Enhancement =**
      - **Pre-contrast → Post-contrast change in Hounsfield Units: >20**
  - **MRI**: Gadolinium
    - Perceptible increase in signal intensity after contrast
    - > 15% signal intensity increase

CT Scan

- **Triple Phase (Renal Mass Protocol)**
  - Pre-contrast
  - Post-contrast (nephrographic phase: ~90 sec)
  - Delayed (10 min)



Tumor Size and Pathology

Tumor Size (cm)	Renal Cancer	Benign*	High Grade
≤2.0	75%	25%	4%
2.1-3.0	80%	20%	5%
3.1-4.0	84%	16%	25%

***Oncocytoma and AML – 75%**

J Urol 2006; 176:896

Kidney Cancer: Evaluation

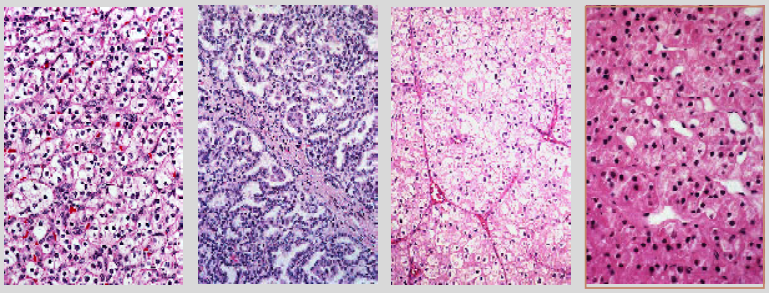
- Detailed H&P
- Laboratory Evaluation:
  - U/A, BMP (Ca++), LFTs, CBC
- Staging:
  - CXR (Chest CT only if large tumor)
  - Bone Scan and/or Brain MRI if clinically indicated
  - No role for PET scan in RCC
- Lung, Bone, Liver most common sites for metastasis at presentation

Renal Cell Carcinoma: Presentation and Survival

Stage at Diagnosis	Distribution	5-yr Survival
Localized	66%	93%
Regional (lymph nodes)	16%	71%
Distant (metastatic)	14%	14%

Seer Database. American Cancer Society. *Cancer Facts & Figures 2022.*

Renal Cell Carcinoma: Histologic Subtypes



Type:	Clear cell	Papillary	Chromophobe	Oncocytoma
Freq (%):	75	15	5	5

Hereditary Renal Cell Carcinoma

Disease	Gene (chromosome)	Histology	Frequency
von Hippel-Lindau	VHL (3)	Clear Cell	75%
HLRCC*	FH (1)	Papillary Type 2	10%
Birt-Hogg-Dube	BHD (17)	Chromophobe/Oncocytoma	10%
Hereditary papillary RCC	Met (7)	Papillary Type 1	5%

*HLRCC = Hereditary Leiomyomatosis Renal Cell Carcinoma

Renal Cell Carcinoma: STAGING

	Stage	Tumor	Lymph Nodes	Metastasis	5 yr Survival
Localized	I	T1 (≤7cm) T1a: ≤ 4cm T1b: >4cm but ≤ 7cm	N0	M0	95%
Localized	II	T2 (>7cm) T2a: >7cm but ≤ 10cm T2b: >10 cm	N0	M0	88%
	III	T1 or T2	N1	M0	59%
	III	T3 (vein/fat) T3a: venous/fat T3b: IVC ↓ diaphragm T3c: IVC ↑ diaphragm	N0 or N1	M0	59%
	IV	T4 (outside Gerota's) Any T	Any N Any N	Any M M1	20%

AJCC 8th Ed. 2016

RCC Prognostic Factors

- **Stage – most important**
- **Grade (1-4)**
  - Grade 1 & 2 more favorable.
- **Histologic sub-type**
  - Papillary type 1 and Chromophobe more favorable
- Molecular biomarkers investigational

Treatment Options

- **Active Surveillance**
- **Needle Ablation (≤ 3cm)**
  - Cryoablation
  - Radiofrequency Ablation
  - Microwave Ablation
- **Surgical Excision**
  - Radical Nephrectomy
  - Partial Nephrectomy

Gold Standard

- **Renal cell carcinoma does NOT respond to standard chemotherapy or radiation***

Role for Renal Mass Biopsy

- Historically, renal masses have not been biopsied.
- Indications:
  - Confirm diagnosis and histologic subtype in patients with metastases or unresectable lesions
  - Non RCC tumor suspected (metastatic/lymphoma etc→ extremely rare)
  - Confirm diagnosis when it would **change treatment**:
    - Prior to ablative therapy
    - Risk adapted management would be considered
      - High surgical risk, baseline CKD, solitary kidney

Active Surveillance

- Candidates:
  - Tumor characteristics:
    - Small size (<3 cm)
    - Tumor growth <5 mm/yr
    - Predominately cystic masses

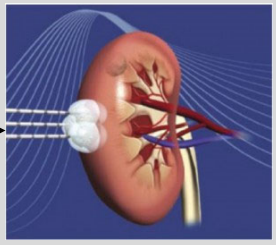
    } **Very low metastatic risk: ~2%**
  - Patient characteristics:
    - Elderly
    - Patients with significant comorbidity unfit for surgery
    - Life expectancy <5 years

Renal Mass Needle Ablation

- Potential for less morbidity/complications
- **Appropriate Candidates for Ablation**:
  - **Solid renal masses ≤ 3cm**
    - Location matters→ posterior peripheral tumors away from important structures ideal
  - **Renal insufficiency**
    - **Ablation has less impact on renal function**
  - Older/comorbid patients who are not good surgical candidates
- Potential for similar efficacy to partial nephrectomy for select masses
  - **Recurrence rates higher after ablation**

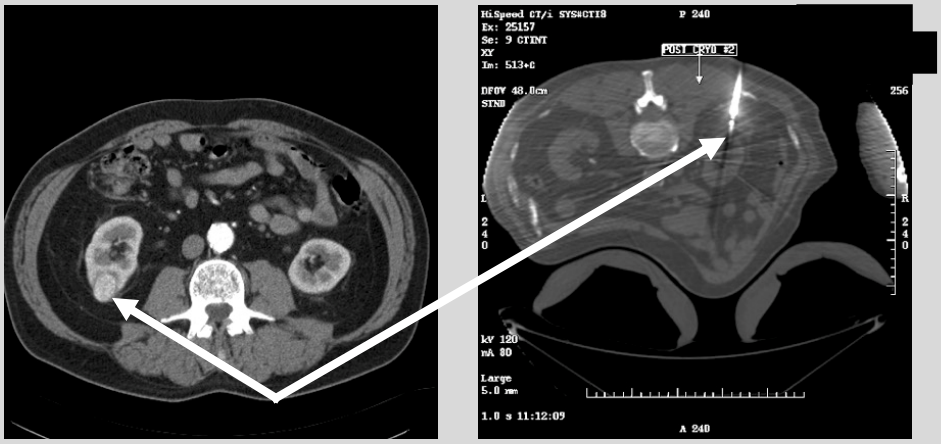
Ablative Modalities

- **Radiofrequency Ablation (RFA)**
- **Cryoablation**
- **Microwave Ablation**



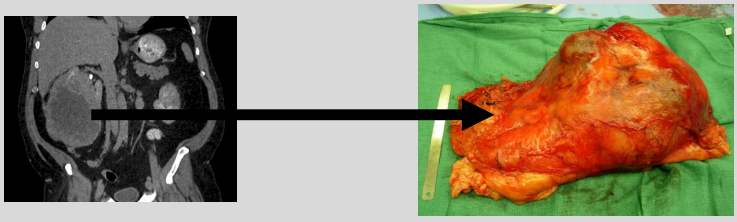
- Typically performed percutaneously with image guidance (CT or U/S).
- Outpatient procedure

Percutaneous Cryoablation



Surgical Excision

- 1) <u>Radical</u> Nephrectomy



- 2) <u>Partial</u> Nephrectomy

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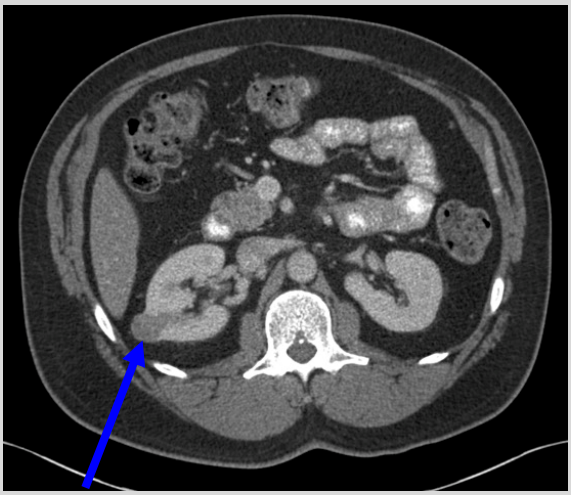
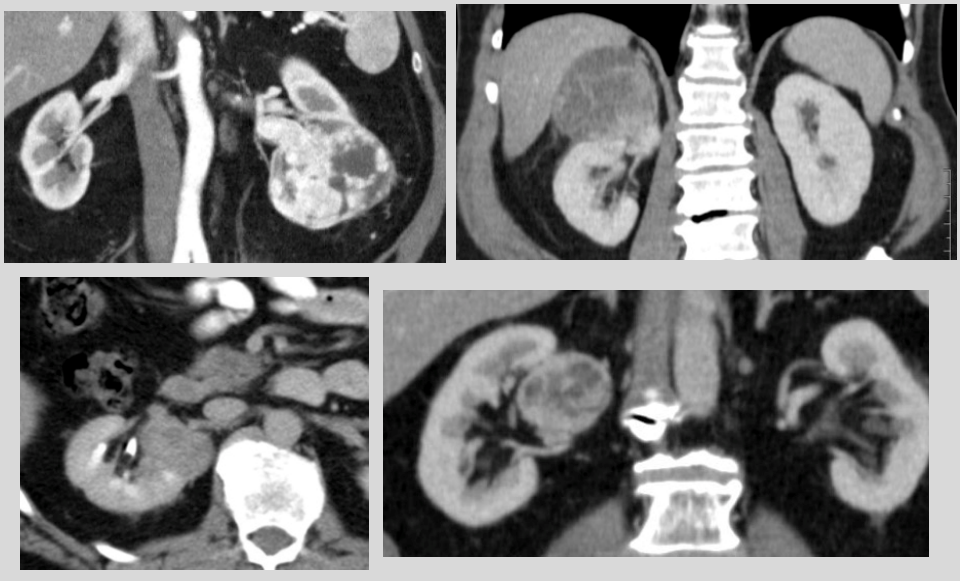
Radical vs Partial Nephrectomy?



Laparoscopic Radical Nephrectomy

Laparoscopic/Robotic surgery is the preferred approach for most tumors

Partial vs. Radical Nephrectomy?



Indications for Partial Nephrectomy

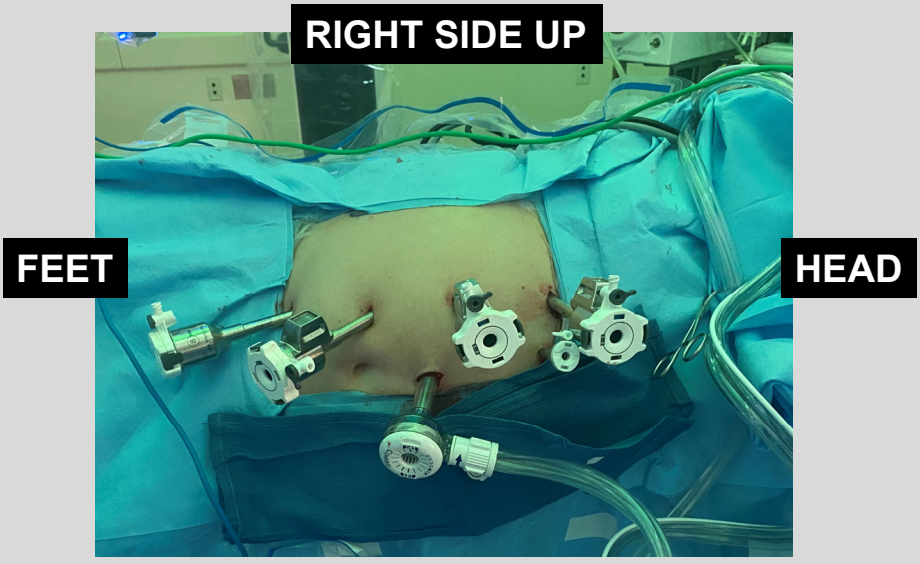
- **Absolute/Imperative:** To prevent anephric state
  - Anatomic/Functional solitary kidney
  - Bilateral RCC
- **Relative:** Contralateral kidney is threatened by local, systemic, genetic conditions that may affect function
  - DM, HTN, stones, VHL
- **Elective:** NSS with a normal contralateral kidney

RENAL TUMOR CONSIDERATIONS

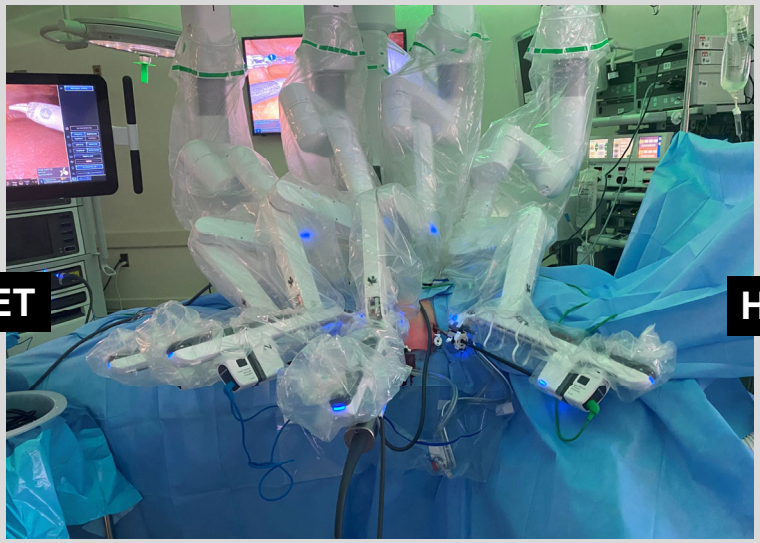
- **1) Partial nephrectomy (PN) oncologically equivalent to radical nephrectomy (RN)**
- **2) Partial nephrectomy has ↓ risk of Chronic Kidney Disease (CKD)**
- **3) Significant morbidity (CV events/death) associated with CKD (GFR<60)**
- **4) Surgical CKD ≠ Medical CKD**
  - **Surgical CKD is stable**
  - **Medical CKD is progressive**
- **5) PN has a ↑ risk of complications**
- **6) Robotic PN equivalent to Open PN with ↓ morbidity**

Robotic Partial Nephrectomy

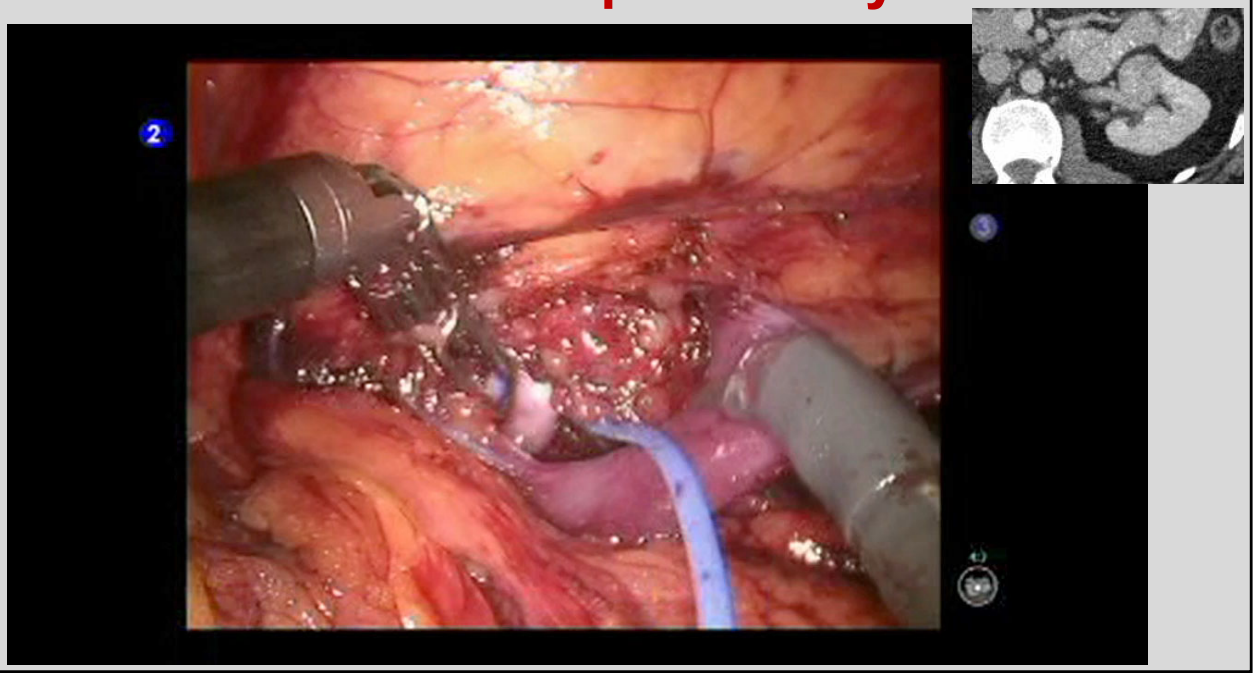
Robotic Partial Nephrectomy



Robotic Partial Nephrectomy

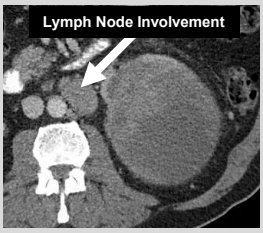


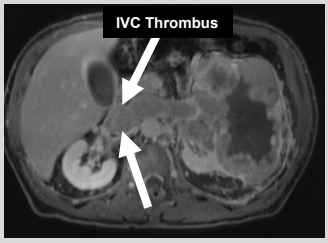
Robotic Partial Nephrectomy



Advanced Disease

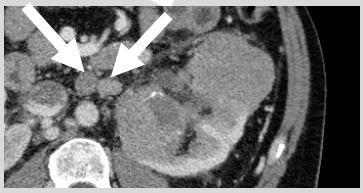
- Surgery remains an integral part of the management of advanced RCC:
  - Tumor thrombus in IVC
  - Regional Lymphadenopathy
  - Adjacent organ involvement
  - Resectable oligometastatic disease



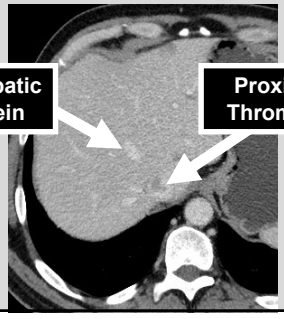


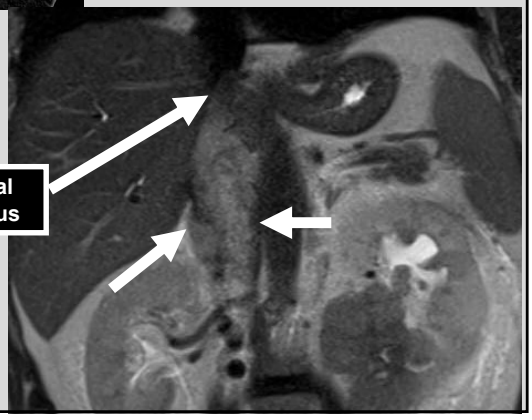
Advanced Stage III RCC

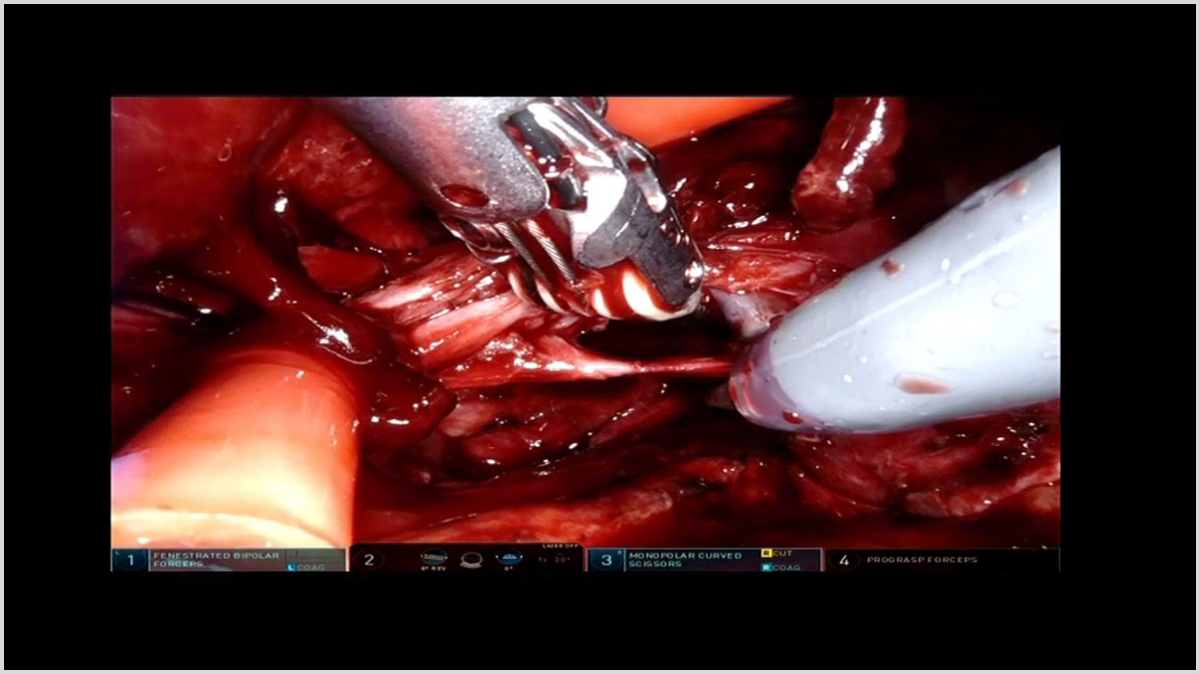
- **Large left renal mass with retroperitoneal adenopathy**



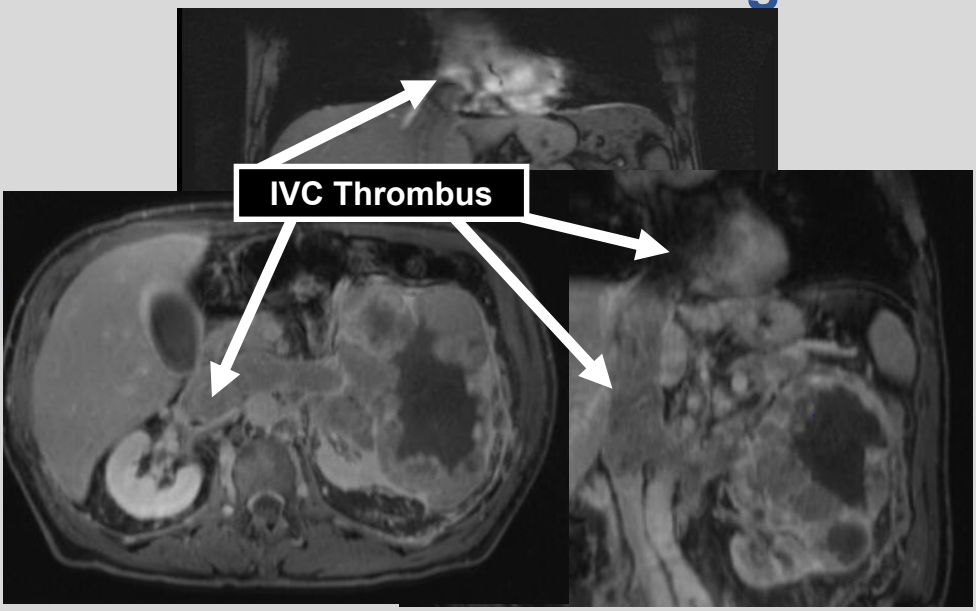
- **IVC tumor thrombus (<u>below</u> hepatic veins).**







16 cm Renal Mass
Level IV Thrombus→ Into Right Atrium



Adjuvant Treatment

- High risk patients after tumor resection.
- Sunitinib & Pembrolizumab are FDA approved.

Inclusion Criteria
-pT2 High Grade
-≥pT3
-pTN+
-M1 NED within 1 yr
-Clear Cell

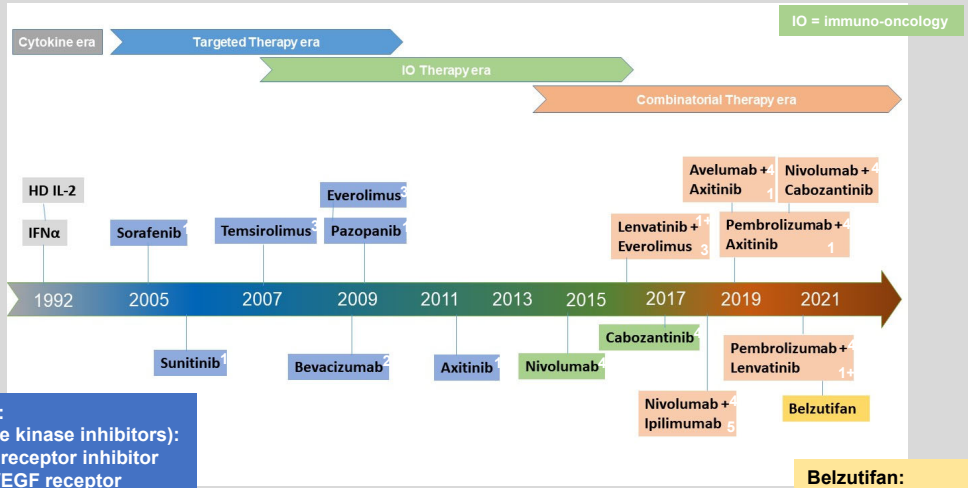
- **Keynote 564** (Pembro X 1 yr):

Disease Free Survival @ 24 months
-Pembro: 77.3%
-Placebo: 68.1%

Overall Survival @ 24 months
-Pembro: 96.6%
-Placebo: 93.5%

NEJM 2021; 385:683

Metastatic Renal Cell Carcinoma



Targeted Therapy:
-TKI (tyrosine kinase inhibitors):
[1]VEGF receptor inhibitor
[2]mab VEGF receptor
-[3]mTOR inhibitor

Immune Checkpoint-Inhibitors:
-[4]PD-1/PD-L1 (anti-programed death receptor 1 and ligand 1)
-[5]CTLA-4 (anti-cytotoxic T lymphocytes antigen-4)

Belzutifan:
-HIF-2α inhibitor
(hypoxia-inducible factor)

Hutson T, Figlin R. The current and evolving therapeutic paradigm in the management of metastatic renal cell carcinoma. *Kidney Cancer Journal*. 2021;19(3). doi: 10.52733/kcj19n3-r1.

Cytoreductive Nephrectomy (CN)

- Nephrectomy in the setting of metastatic disease
- Historically shown to improve overall survival
- Newer agents more active against RCC
- Recent RCT Trials question historical practice:
  - CARMENA → **Median Overal Survival (n=450):**
    →Nephrectomy + sunitinib: 13.9 mo
    →Sunitinib alone: 18.4 mo
    NEJM 2018; 379: 417
  - SURTIME → **Median Overal Survival (n=99):**
    →Immediate CN: 15.0 mo
    →Sunitinib → Deferred CN: 32.4 mo
    JAMA Onc 2018; 5:164

Cytoreductive Nephrectomy

- What do we do in 2022?
- Patient selection is key→ **minimize time off systemic treatment**
  - **Consider upfront cytoreductive nephrectomy:**
    - Good performance status/surgical candidate
    - Low Volume, Oligometastatic mRCC (esp if lung only)
  - Others get upfront systemic therapy
    - Ongoing trials to answer the role of CN in current era.

Metastatic RCC

Risk*	Preferred**
Favorable- Clear Cell	▪ Axitinib + Pembrolizumab ▪ Cabozantinib + Nivolumab ▪ Lenvantinib + Pembrolizumab
Poor/Intermediate- Clear Cell	▪ Axitinib + Pembrolizumab ▪ Cabozantinib + Nivolumab ▪ Ipilimumab + Nivolumab ▪ Lenvantinib + Pembrolizumab ▪ Cabozantinib
Non Clear Cell	▪ Clinical Trial ▪ Cabozantinib ▪ Sunitinib

*IMDB Risk Model
**NCCN 2022 Guidelines

Metastatic RCC

- **Immunotherapy based combination therapy**
  - Objective response rates as high as 71%[1]
  - Median overall survival as long as 4+ years[2]
  - Complete response rates as high as 16%[1]

[1]NEJM 2022; 384:1289
[2]ESMO Open. 2020;5:e001079

CONCLUSION

- Kidney cancer represents a large spectrum of disease
- Most solid renal masses represent renal cell carcinoma but there is a role for biopsy in selected cases
- Most surgery can be performed in a minimally invasive fashion (laparoscopic/robotic)
- Partial nephrectomy should be prioritized when technically feasible.
- Changing paradigms with adjuvant treatment & cytoreductive surgery
- Major advances have occurred with treatment of metastatic RCC.