# Bladder Cancer

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MedNet21
Center for Continuing Medical Education

The Ohio State University Wexner Medical Center

## 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**

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## 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

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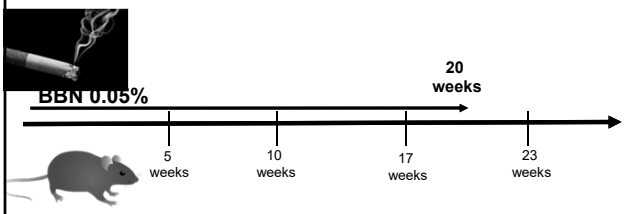
The Ohio State University Comprehensive Cancer Center
Laboratory Startup

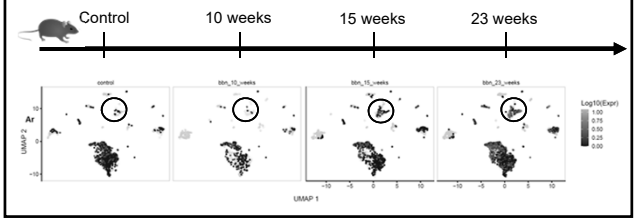
Consulting/Honoraria:
Research Square
Janssen
Arquer
SurvivorNet

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




**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?**

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# 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) |

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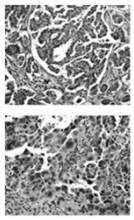
## Tumor grade

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



← **Low** grade

← **High** grade

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## 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) |

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## Bladder cancer M stage

- M0-1

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

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## 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

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## 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?

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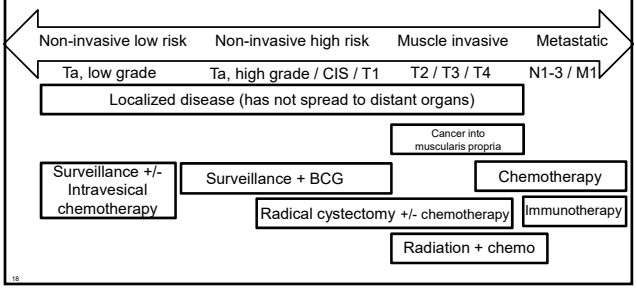
## Bladder Cancer treatment depends on grade & stage

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## 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

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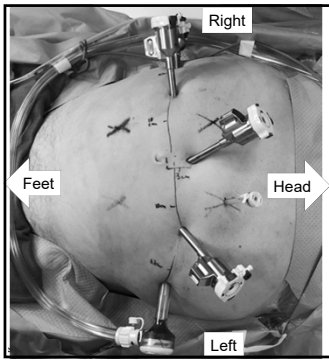
## What did my patient do?

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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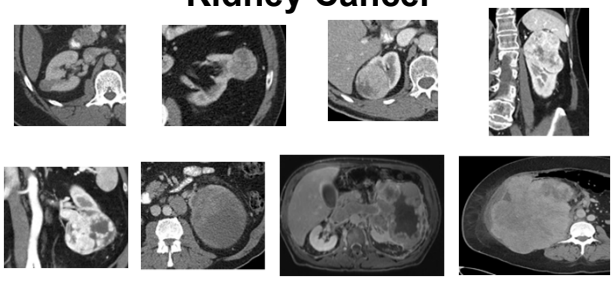
## Kidney Cancer: Outline

- **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

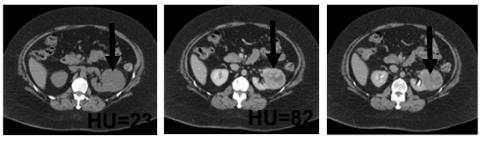
| Tissue | HU |
|---|---|
| Bone | +1000 |
| Blood | 40 |
| Kidney | 30 |
| Water | 0 |
| Fat | -50 |
| Air | -1000 |

## 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

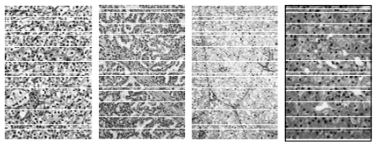
- Detailed H&P
- Laboratory Evaluation:
  - U/A, BMP (Ca++), LFTs, CBC
- Staging:
  - CXR (Chest CT only if large tumor)
  - Bone Scan and/or Brain MRI if clinically indicated
  - No role for PET scan in RCC
- Lung, Bone, Liver most common sites for metastasis at presentation

## 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



| | Clear cell | Papillary | Chromophobe | Oncocytoma |
|---|---|---|---|---|
| Type: | | | | |
| 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)<br>T1a: ≤ 4cm<br>T1b: >4cm but ≤ 7cm | N0 | M0 | 95% |
| Localized | II | T2 (>7cm)<br>T2a: >7cm but ≤ 10cm<br>T2b: >10 cm | N0 | M0 | 88% |
| | III | T1 or T2<br>T3 (vein/fat)<br>T3a: venous/fat<br>T3b: IVC ↓ diaphragm<br>T3c: IVC ↑ diaphragm | N1<br>N0 or N1 | M0 | 59% |
| | IV | T4 (outside Gerota's)<br>Any T | Any N<br>Any N | Any M<br>M1 | 20% |

## 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** ← **Gold Standard**
  - Radical Nephrectomy
  - Partial Nephrectomy
- **Renal cell carcinoma does NOT respond to standard chemotherapy or radiation***

## Role for Renal Mass Biopsy

- Historically, renal masses have <u>not</u> been biopsied.
- <u>Indications</u>:
  - 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 **<u>change treatment</u>**:
    - 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

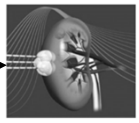
    → **Very low metastatic risk: ~2%**
  - Patient characteristics:
    - Elderly
    - Patients with significant comorbidity unfit for surgery
    - Life expectancy <5 years

## 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**

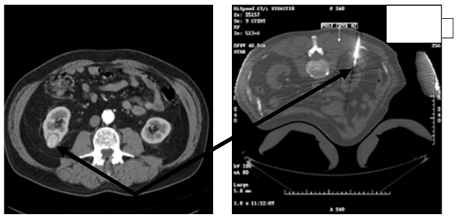
## Ablative Modalities

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



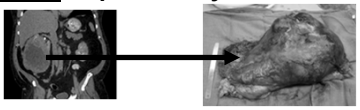
- Typically performed percutaneously with image guidance (CT or U/S).
- Outpatient procedure

## Percutaneous Cryoablation

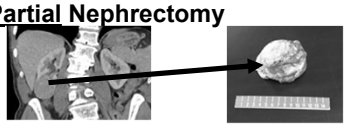


## Surgical Excision

- **1) Radical Nephrectomy**



- **2) Partial Nephrectomy**



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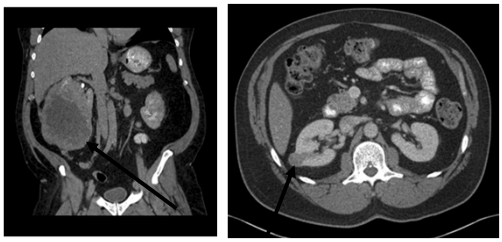
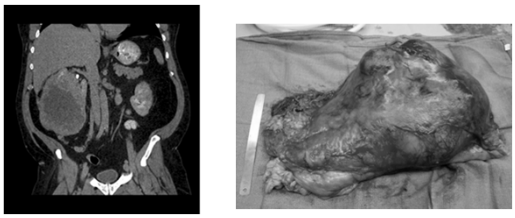
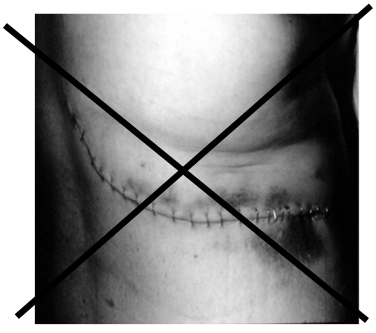
## Radical vs Partial Nephrectomy?



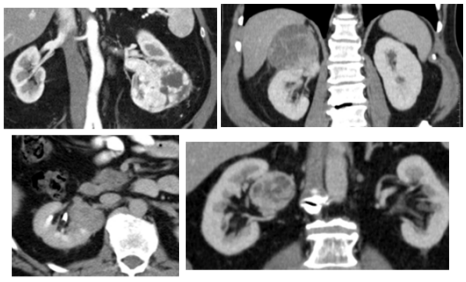
## Laparoscopic Radical Nephrectomy

**Laparoscopic/Robotic surgery is the preferred approach for most tumors**





## Partial vs. Radical Nephrectomy?



# Indications for Partial Nephrectomy

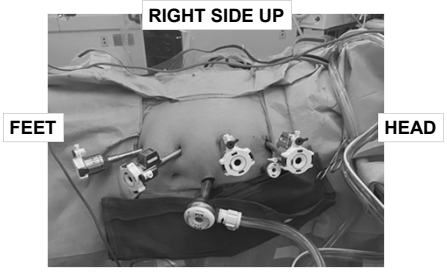
- **Absolute/Imperative:** To prevent anephric state
  - Anatomic/Functional solitary kidney
  - Bilateral RCC
- **Relative:** Contralateral kidney is threatened by local, systemic, genetic conditions that may affect function
  - DM, HTN, stones, VHL
- **Elective:** NSS with a normal contralateral kidney

# 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**

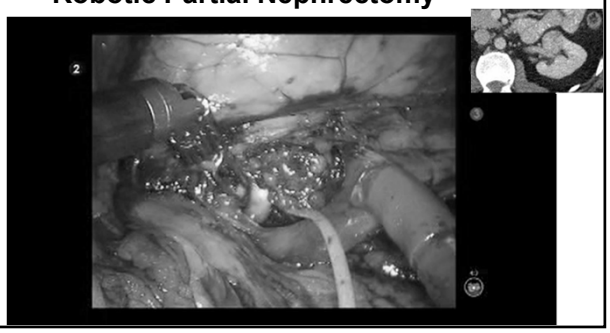
# Robotic Partial Nephrectomy

# Robotic Partial Nephrectomy



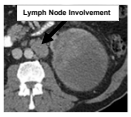
## Robotic Partial Nephrectomy

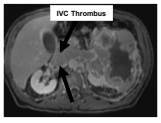

## Robotic Partial Nephrectomy



## Advanced Disease

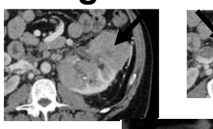
- Surgery remains an integral part of the management of advanced RCC:
  - Tumor thrombus in IVC
  - Regional Lymphadenopathy
  - Adjacent organ involvement
  - Resectable oligometastatic disease

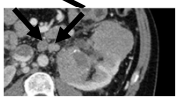



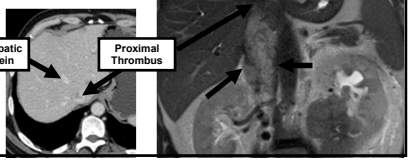

## Advanced Stage III RCC

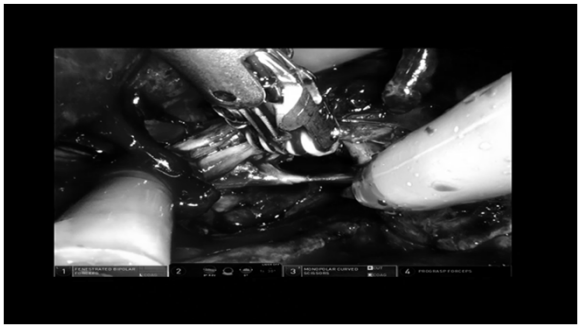
- **Large left renal mass with retroperitoneal adenopathy**



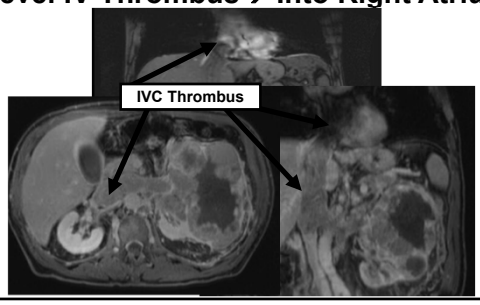


- **IVC tumor thrombus (<u>below</u> hepatic veins).**





## 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

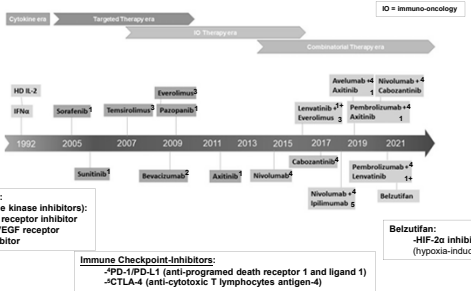
- **Keynote 564** (Pembro X 1 yr):

**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




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<br>• Cabozantinib + Nivolumab<br>• Lenvantinib + Pembrolizumab |
| Poor/Intermediate- Clear Cell | • Axitinib + Pembrolizumab<br>• Cabozantinib + Nivolumab<br>• Ipilimumab + Nivolumab<br>• Lenvantinib + Pembrolizumab<br>• Cabozantinib |
| Non Clear Cell | • Clinical Trial<br>• Cabozantinib<br>• 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.