

# Stereotactic Body Radiation Therapy for Primary Renal Cell Carcinoma in Inoperable Patients

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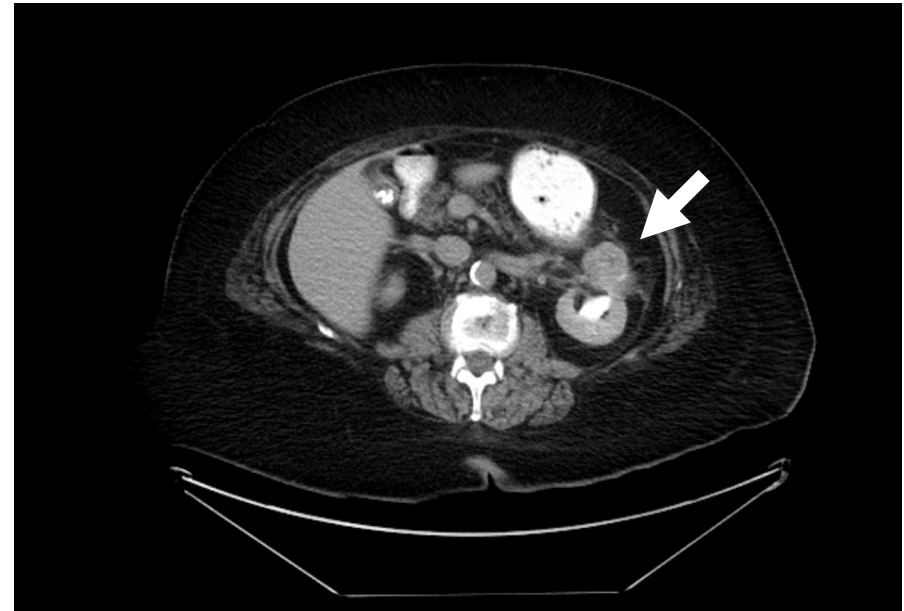
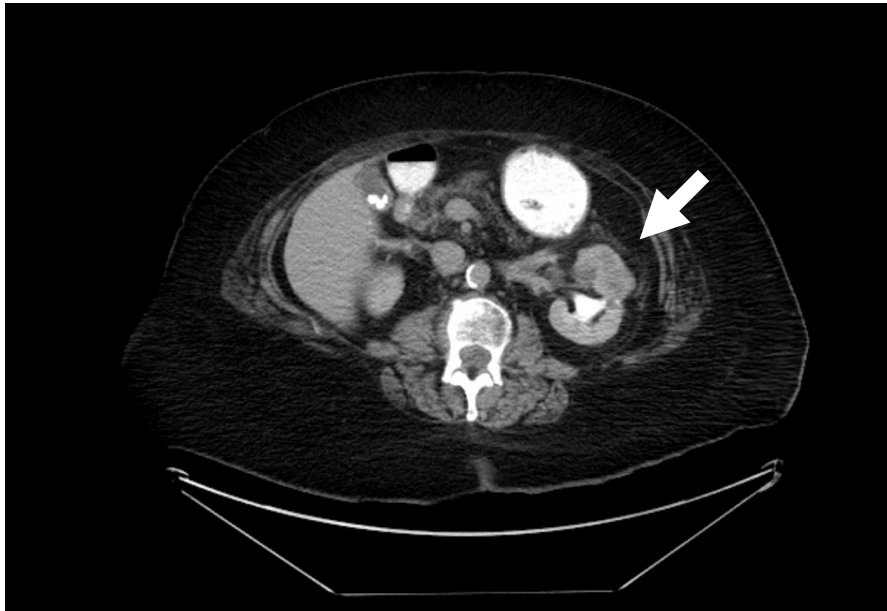
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# ARROCase: Clinical presentation

- **HPI:** Woman in her early 70s who presents to urology with gross hematuria
- **PMH/PSH:** HTN, DM
- **Social History:** 30 pack-year former smoker (quit 2 years ago), no known occupational exposures
- **Family History:** No family history of cancer

# ARROCase: Initial evaluation

- **Cystoscopy:** No lesions in the bladder, but atypical cells on cytology
- **CT CAP w/ Contrast** demonstrating a left upper pole mass suggestive of RCC, described as, “...mild exophytic solid left renal lesion. the bulk of the mass measures maximum diameter of 4 cm which is homogenously enhancing. A more medial component of this mass appears to insinuate into the renal pelvis based on its appearance.”



# ARROCase: Initial evaluation

- **CT Guided Biopsy** demonstrating clear cell renal cell carcinoma (ccRCC)
- **Renal function scan** with mild impairment of tubular function in the kidneys bilaterally. The left kidney does not empty completely after furosemide administration.
- **Outpatient urology consultation:**
  - Surgical resection recommended, but patient declined
- **Outpatient radiation oncology consultation:**
  - Surgery emphasized as standard-of-care, but given patient refusal SBRT versus moderately hypofractionated radiation offered
  - Patient elected to proceed with SBRT

# Renal Cell Carcinoma: Epidemiology<sup>1</sup>

- In the United States in 2020:
  - 73,750 estimated new cases (4.1% of new cancer cases)
  - 14,830 estimated deaths (2.4 % of all cancer deaths)
  - 8<sup>th</sup> most common cancer diagnosis
    - Incidence increased over past 50 years, stable since 2008 - 2017
- 65% diagnosed with localized disease, 16% regional disease, and 16% distant disease
- 5-year relative survival of 75.2% (from 2010 – 2016)
  - Localized: 92.5% 5-year survival
  - Regional: 70.4% 5-year survival
  - Distant: 13% 5-year survival

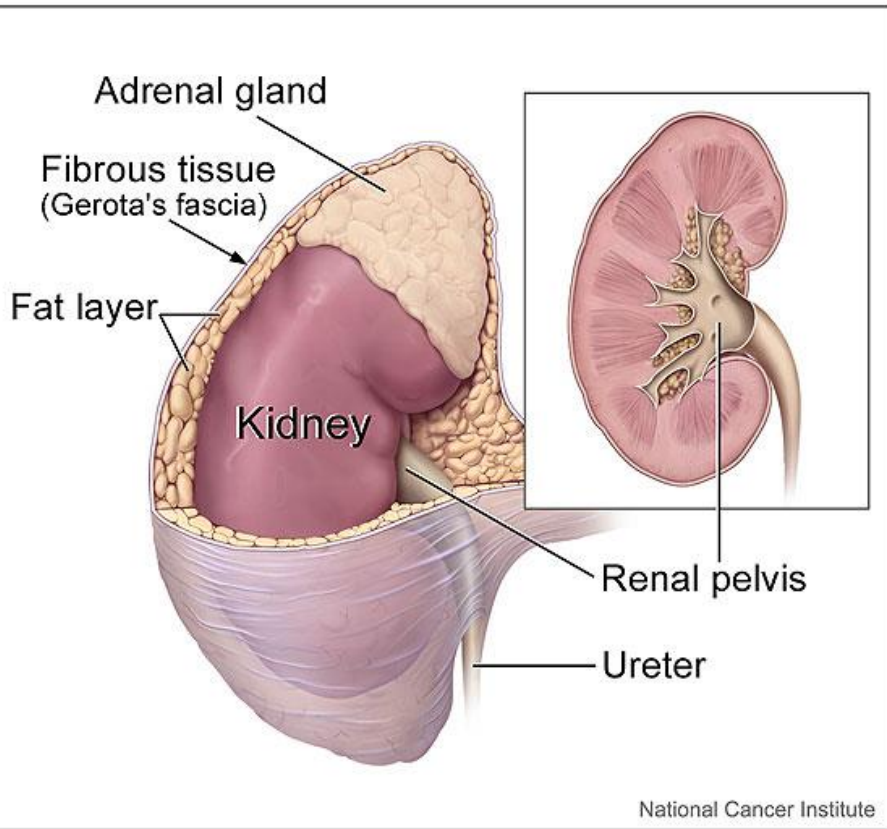
# Risk Factors<sup>2</sup>

- **Age** (64 median age at diagnosis)
  - Most patients diagnosed between ages 65 – 74
- **Sex** (2 of 3 cases in males)
- **Race**
  - Highest incidence in American Indian/Alaska Native
  - Lowest incidence in Asian/Pacific Islander
- **Smoking** (1.5 – 1.6 RR of advanced disease)<sup>3</sup>
- **Alcohol**
- **Obesity**
- **Poorly-controlled hypertension**
- **Kidney stones**<sup>4</sup>
- **Occupational exposures:** benzene, vinyl chloride, coal tar, mineral oil, cadmium, herbicides, pesticides<sup>5</sup>
- **Acetaminophen**<sup>6</sup>

# Genetic Syndromes

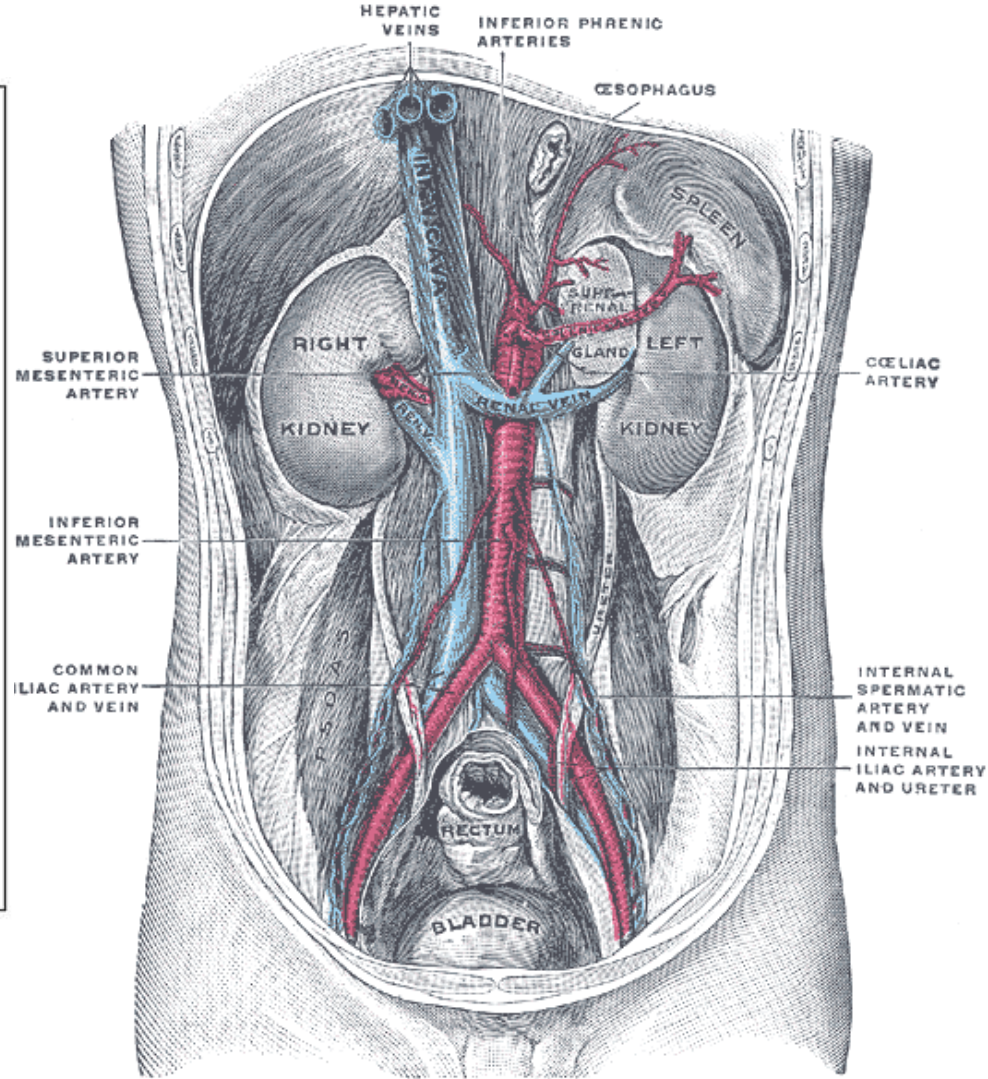
- **Von Hippel-Lindau syndrome**
  - Mutation in **VHL tumor suppressor gene**, inherited in an autosomal dominant pattern
  - **VHL regulates hypoxic inducible factor (HIF1 $\alpha$ )**
  - Predisposes to formation of cysts and tumors in central nervous system, retina, adrenal glands, pancreas, kidneys, epididymis (men), broad ligament (women)
  - Predominantly clear cell RCC (ccRCC), which develops in up to 2 of 3 patients, may be bilateral<sup>7</sup>
- **Tuberous sclerosis<sup>8</sup>**
  - Mutations in either **TSC1 (hamartin protein)** or **TSC2 (tuberin protein)** tumor suppressor genes, inherited in an autosomal dominant pattern
  - **TSC1 and TSC2 regulate the mTOR signaling pathway**
  - RCC occurs in 2-5% of patients with tuberous sclerosis
  - Most often ccRCC, but also associated with papillary renal cell carcinoma and hybrid oncocytic/chromophobe (HOCT) tumors

# Anatomy



[National Cancer Institute](#)

By: Alan Hoofring, Public Domain

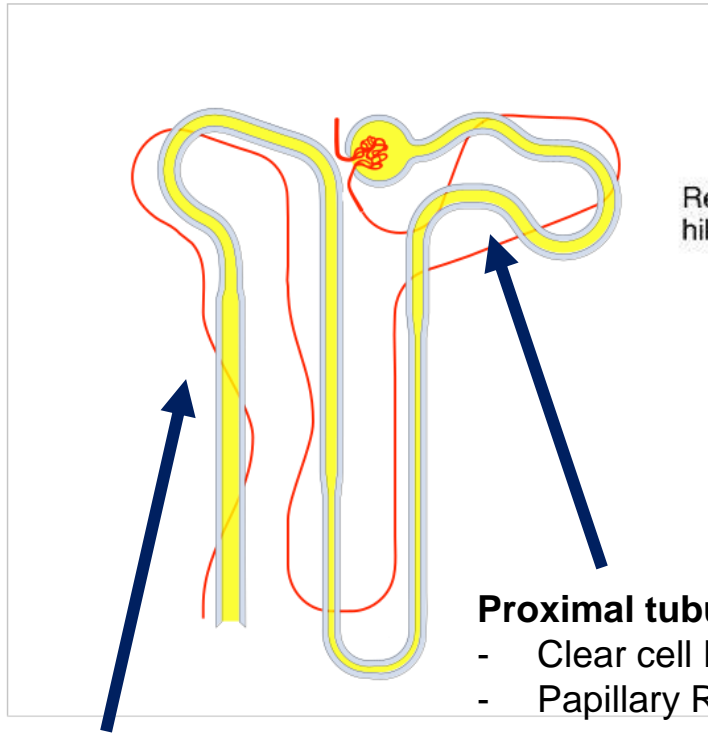


[By Henry Vandyke Carter - Henry Gray \(1918\) Anatomy of the Human Body, Bartleby.com: Gray's Anatomy, Plate 1121, Public Domain](#)



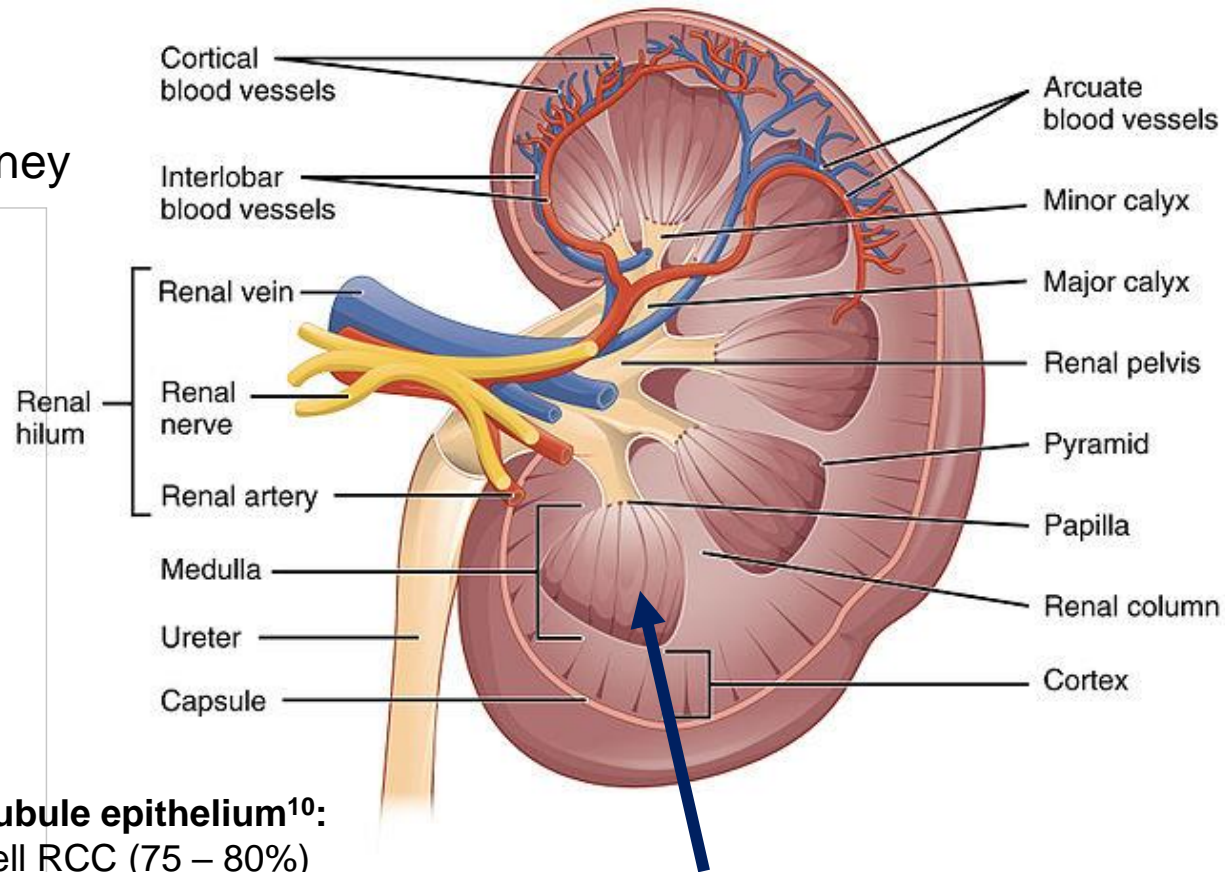
# Anatomy

## Nephron: functional unit of kidney



## Distal nephron/collecting tubule<sup>10</sup>:

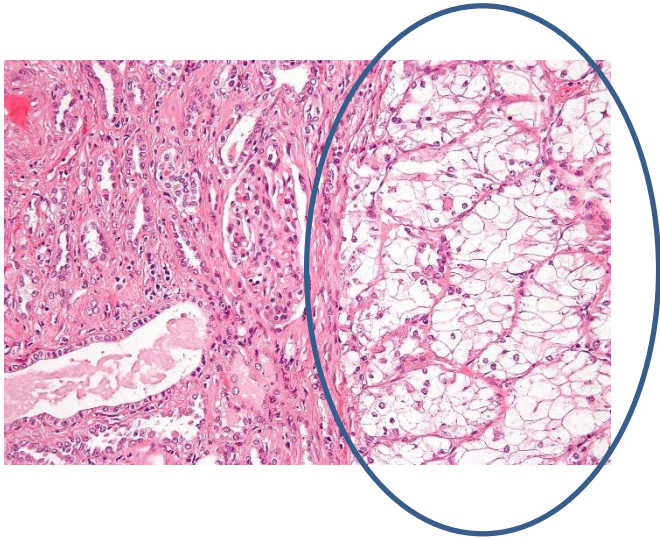
- Chromophobe RCC (5%)
- Collecting duct RCC (< 1%)



**Source:** Anatomy & Physiology, Connexions Web site. <http://cnx.org/content/col11496/1.6/>, Jun 19, 2013  
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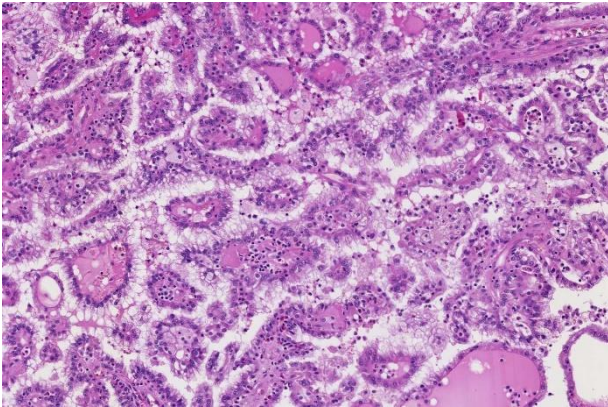
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# Histology



## **Clear Cell Renal Cell Carcinoma<sup>11</sup>**

- Compact nests and sheets of cells with clear cytoplasm and distinct membrane
- Arborizing thin-walled vessels
- Patterns: solid, alveolar (nested), acinar (tubular), microcystic or macrocystic

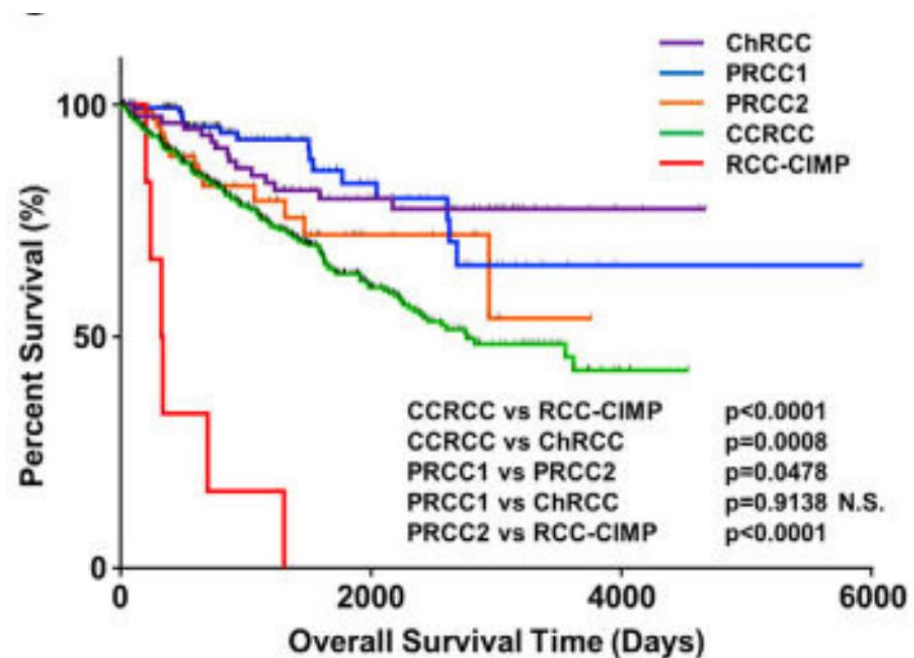
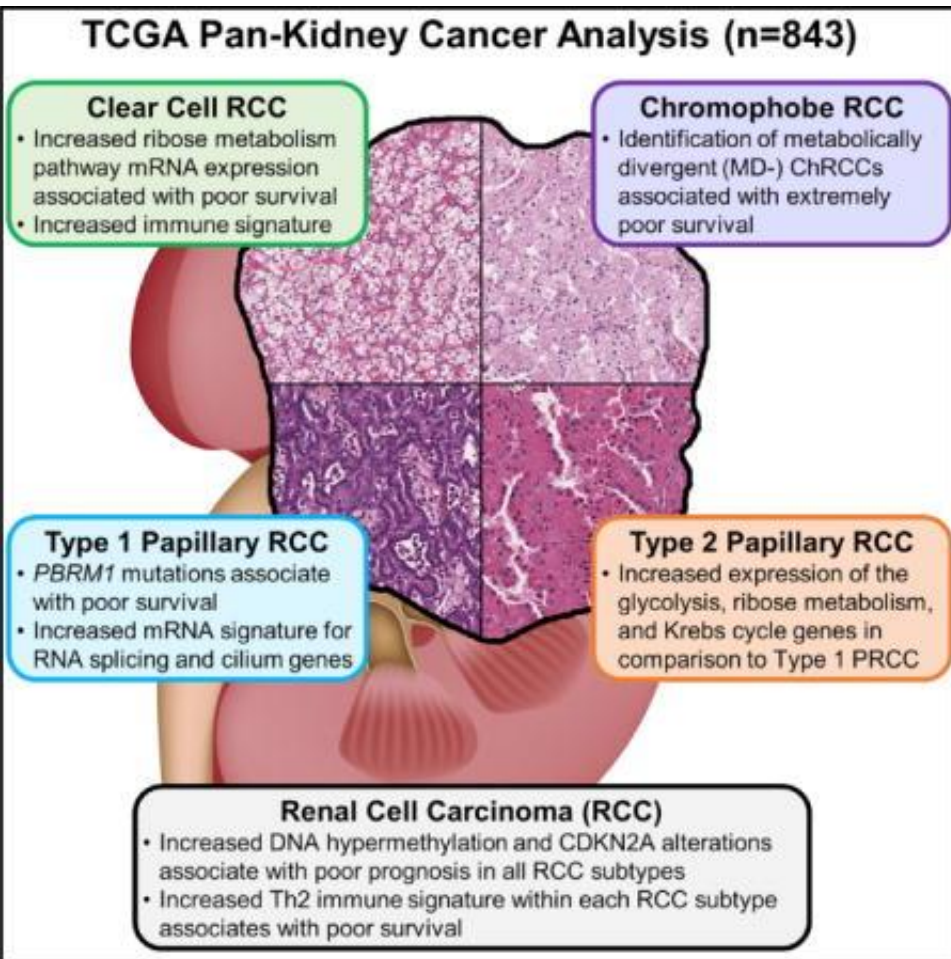


## **Papillary Renal Cell Carcinoma<sup>12</sup>**

- Often circumscribed with pseudocapsule
- Papillae or tubulopapillary architecture with fibrovascular cores
- May contain foamy macrophages, psammoma bodies, hemosiderin

Sources: [https://commons.wikimedia.org/wiki/File:Clear\\_cell\\_renal\\_cell\\_carcinoma\\_high\\_mag.jpg](https://commons.wikimedia.org/wiki/File:Clear_cell_renal_cell_carcinoma_high_mag.jpg) (<https://creativecommons.org/licenses/by-sa/3.0/deed.en>),  
[https://commons.wikimedia.org/wiki/File:Histopathology\\_of\\_papillary\\_renal\\_cell\\_carcinoma\\_type\\_1.jpg](https://commons.wikimedia.org/wiki/File:Histopathology_of_papillary_renal_cell_carcinoma_type_1.jpg) (<https://creativecommons.org/licenses/by/4.0/deed.en>)

# The Cancer Genome Atlas: Molecular Profiling<sup>13</sup>



# Clinical Presentation<sup>14</sup>

- **Asymptomatic**, discovered incidentally on imaging for other indications (better prognosis)
- **Hematuria, flank pain, abdominal mass** (classic triad suggests advanced disease)
- **Scrotal varices** (left-sided predominance)
- **IVC involvement** with lower extremity edema, ascites, pulmonary emboli, hepatic dysfunction, Budd-Chiari syndrome
- Symptoms related to **metastases** (lungs, lymph nodes, bone, liver and brain)

# Paraneoplastic Syndromes<sup>14</sup>

- **Anemia** (iron-studies consistent with ACD)
- **Fever**
- **Cachexia**
- **Hepatic dysfunction** (Stauffer syndrome if no liver metastases, possibly related to tumor cytokine production)
- **Hypercalcemia** (lytic bone metastases, PTHrP production, prostaglandins → bone resorption)
- **Erythrocytosis** (erythropoietic production)
- **Secondary amyloidosis** (chronic inflammatory response)
- **Thrombocytosis** (unclear mechanism)
- **Polymyalgia rheumatica** (not steroid responsive, may respond to nephrectomy)

# Diagnostic Evaluation<sup>9,14</sup>

- H&P
- Labs: CBC with differential, CMP, UA
- Abdominal CT
- Abdominal MRI if CT inconclusive, or for further evaluation of invasion of blood vessels and/or collecting system
- **No biopsy if undergoing partial or radical nephrectomy**
  - NCCN states that biopsy of small lesions may confirm diagnosis of malignancy for surveillance or ablative techniques
    - Biopsy may also be appropriate when urothelial carcinoma or lymphoma is possible or suspected
- **If inoperable, potential biopsy of primary to guide medical therapy**
- **If metastatic, biopsy of metastatic lesion preferred**
- Chest CT or radiograph
- Bone scan (if pain or elevated alkaline phosphatase)
- Genetic evaluation
  - ≤ 46 years old, close family history of kidney cancer, or multiple renal masses)

# Imaging Characteristics<sup>15</sup>

## CT

- Small lesions may enhance homogeneously
- Larger lesions may have irregular enhancement due to areas of necrosis
- 30% with calcification
- 5-15% intraluminal growth into renal vein
- Prognosis worse for IVC involvement

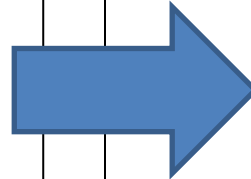
## MRI

- T1 heterogeneous
  - Blood, necrosis, solid components
- T2 depends on histology
  - ccRCC: hyperintense
  - Papillary RCC: hypointense
- T1 contrast (Gd): arterial enhancement
- Distinguishes between bland and tumor thrombus in vessels

# International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) Criteria

## Prognostic Factors

1. < 1 year from diagnosis to systemic therapy
2. PS < 80% (Karnofsky)
3. Hgb < lower limit normal (12 g/dL)
4.  $\text{Ca}^{2+}$  > ULN (10.2 mg/dL)
5. Neutrophil > ULN ( $7 \times 10^9/\text{L}$ )
6. Platelets > ULN (400,000)



## Prognostic Risk Groups

- Favorable = 0 risk factors
- Intermediate = 1 – 2 risk factors
- Poor = 3 – 6 risk factors



# AJCC 8<sup>th</sup> Edition TNM Staging

## T1

- **T1a:** ≤ 4 cm, limited to kidney
- **T1b:** > 4 cm but ≤ 7 cm, limited to kidney

## T2

- **T2a:** > 7 cm but ≤ 10 cm limited to kidney
- **T2b:** > 10 cm limited to kidney

## T3

- **T3a:** extends to renal vein, pelvicalyceal system, perirenal or renal sinus fat, but not beyond Gerota's fascia
- **T3b:** Extends into vena cava below diaphragm
- **T3c:** Extends into the vena cava above the diaphragm or invades wall of vena cava

## T4

- **T4:** Invades beyond Gerota's fascia (including extension to ipsilateral adrenal gland)

## N0

- No regional lymph node metastases

## N1

- Involved regional lymph node(s)

## M0

- No metastases

## M1

- Distant metastases

## Prognostic Groups

Stage I = T1 N0M0

Stage II = T2 N0M0

Stage III = T1-2 N1M0 & T3 NX,N0-N1M0

Stage IV = T4 Any N, Any T/N M1

# Treatment Options<sup>9</sup>

- **Surgery**
  - Partial nephrectomy (preferred treatment for T1a & T1b)
  - Radical nephrectomy
- **Ablative Techniques** (T1a tumors)
  - Radiofrequency Ablation
  - Cryotherapy
- **Active surveillance** (T1 patients with significant risk of morbidity or death from intervention, small unbiopsied renal masses < 2 cm that may be benign, or predominantly cystic T1a masses)
- **SBRT** (reserved for inoperable patients or those who decline surgery)
  - Alternatively, moderately hypofractionated radiation (i.e. palliative intent)
- **Systemic Treatment**
  - Immunotherapy
  - Targeted therapy

# NCCN Treatment Guidelines<sup>9</sup>

- NCCN Treatment Kidney Cancer Guidelines v4.2021 **does not** include SBRT as a treatment strategy for primary RCC
- No discussion of SBRT for inoperable or medically unfit patients
- No discussion of SBRT for use in cytoreductive therapy
- SBRT is a Category 2A recommendation for treatment of metastatic lesions

# Efficacy of SBRT for RCC

- RCC **was** considered radioresistant based on *in vitro* data and results of 1970s/1980s clinical trials that used conventionally fractionated radiation and failed to show a benefit with neoadjuvant or adjuvant regimens
- Early experience with SBRT to metastatic lesions demonstrated high rates of local control, suggesting RCC is responsive to high BED radiation (next slide)

# Efficacy of SBRT for RCC

## Extracranial stereotactic radiotherapy for primary and metastatic renal cell carcinoma<sup>16</sup>

### Patient population and intervention:

- 58 patients with 162 lesions treated with SBRT (lung metastases most common)
- 50 patients with metastatic disease and 8 patients with primary or inoperable recurrent disease
- Most common fractionation schedules: 8 Gy x4, 10 Gy x4, & 15 Gy x3
- Co-planar or non-coplanar conformal static fields with CT verification

### Results:

- 30% of lesions with complete regression, 60% with partial regression or no change
- 3 local recurrences, local control of ~ 90% with median follow-up of 13 – 37 months
- Majority of patients developed new metastatic lesions and many were re-treated to new sites of metastatic disease, with suggested survival benefit

### Adverse events:

- 23 of 58 patients with adverse effects
  - 50% Grade I-II, and most common cough, nausea, and pain
  - 5x patients requiring steroid treatment for radiation pneumonitis
  - 1x Grade 5 gastric hemorrhage after treatment for pancreatic metastasis

# Radiation for Primary RCC

## Pooled analysis of SABR for primary RCC: A report from the International Radiosurgery Oncology Consortium for Kidney (IROCK)<sup>17</sup>

### Patient population and intervention:

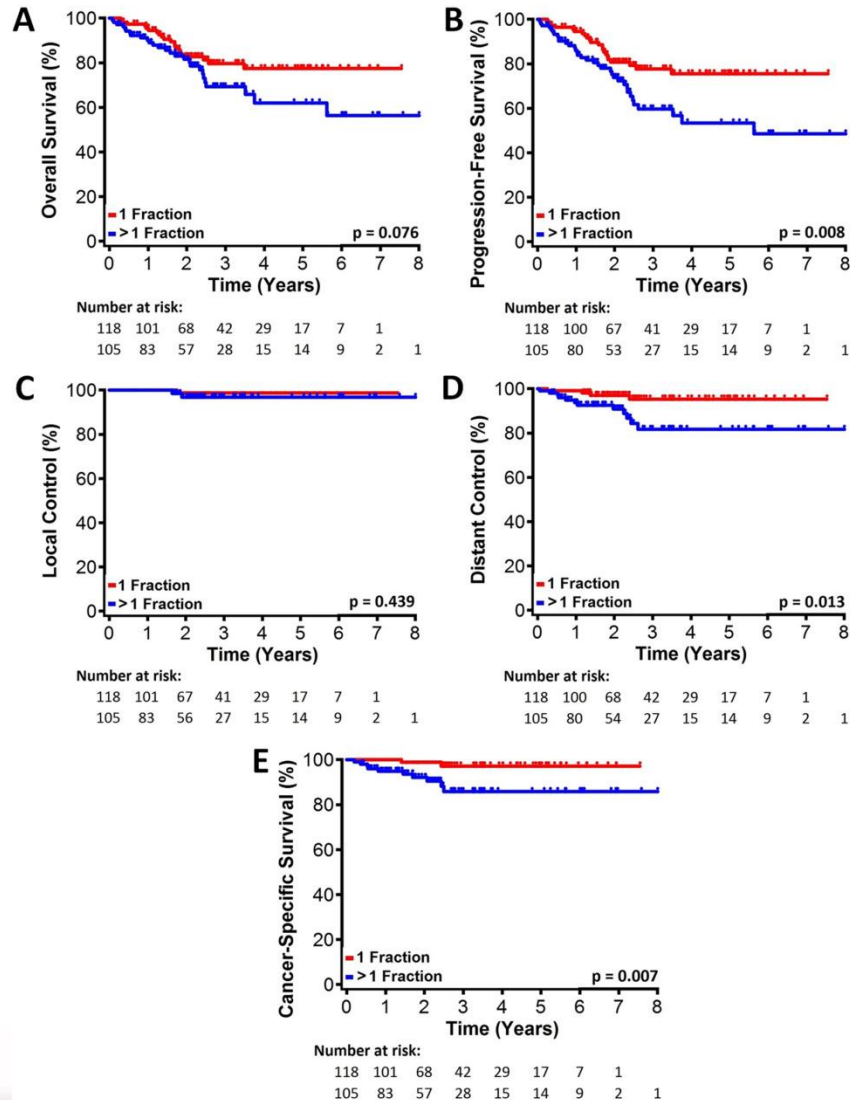
- 223 patients from 9 institutions
- 70% male, and mean age of 72
- Mean maximal tumor dimension of 43.6 mm +/- 27.7 mm
- 118 patients received single-fraction SBRT (median BED 87.5 Gy) and 105 patients received multi-fraction SBRT (median BED 80 Gy). Dose range of 14-26 Gy, median of 25 Gy.
  - Patients receiving single-fraction SBRT were younger, had better performance status, and had smaller tumors

### Results:

- Local control at 2 & 4 years = 97.8%
- 2-year: CSS = 95.7%, OS = 82.1%, PFS = 77.4%
- 4-year: CSS = 91.9%, OS = 70.7%, PFS = 65.4%
- 3 patients with local recurrence, 16 with distant recurrence (1 of with both local and distant)
- Mean change in eGFR - 5.5 +/- 13.3 mL
- Larger maximum tumor size and multi-fraction SBRT associated with inferior CSS and PFS in both regimens
- Larger maximum tumor size associated with worse OS

### Adverse events:

- 36% with Grade 1 or 2 toxicity only (nausea more common in single-fraction 17% versus 6.8%)
- 1 patient with Grade 3 nausea and Grade 2 bowel toxicity
- 1 patient with Grade 4 bowel toxicity
- 1 patient with Grade 4 gastritis, followed by Grade 4 bowel toxicity



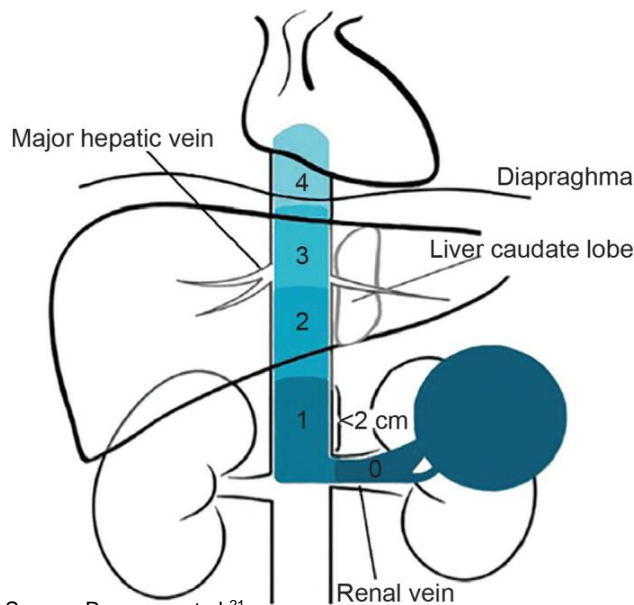
# Scenarios using SBRT for Primary RCC

- Efficacious for tumors  $> 4$  cm (T1b) when ablative therapies may be difficult to employ<sup>18</sup>
- Feasible and safe for treatment of solitary kidney tumors<sup>19</sup>
- Demonstrated success in treating tumors with IVC tumor thrombus (next slide)

# Inferior Vena Cava Tumor Thrombus

- **Inferior vena cava tumor thrombus (IVC-TT)**
  - Level 3 and 4 tumor thrombus may involve more extensive surgical resection with increased morbidity
  - Patients with comorbidities may not be candidates for surgical resection of advanced lesions

- **SBRT used successfully to treat patients with IVC-TT<sup>20</sup>**
  - Of 2 patients reported in literature:
    - One patient demonstrated ongoing response at 24 months after treatment to level 4 recurrent IVC-TT lesion
    - One patient with metastatic disease and level 4 IVC-TT had better than expected clinical course with 18-month survival after treatment



Source: Ramazan et al.<sup>21</sup>

## Mayo Clinic RCC Tumor Thrombus Classification

Level	Definition
0	Limited to renal vein or its tributaries
1	Extends into IVC < 2 cm above renal vein orifice
2	Extends into IVC > 2 cm above renal vein orifice, but below hepatic veins
3	Extends above hepatic veins but below diaphragm
4	Extends above diaphragm



# Ongoing Phase II Clinical Trials

## [NCT02141919](#): SABR for Patients with Primary Renal Cancer

- **Estimated enrollment:** 16 patients
- **Inclusion:** Biopsy proven renal cancer  $\leq 5$  cm with growth  $\geq 2$  mm in a 1-year period
- **Exclusion:** No prior abdominal radiation, RFA, cryoablation or evidence of metastatic disease for  $\geq 3$  years prior to registration
- **Technique:** 12 Gy in 3 fractions, 10 Gy in 4 fractions, 8 Gy in 5 fractions
- **Primary outcome:** 2-year tumor growth and viability
- **Secondary outcomes:** Growth rate, renal function, disease progression, adverse events

## [NCT01890590](#): A Phase II Study of Cyberknife Radiosurgery for RCC

- **Estimated enrollment:** 46 patients
- **Inclusion:** Biopsy proven T1N0M0 RCC  $\leq 8$  cm, serum creatinine  $< 3$  mg/dL, no coagulopathy, no transaminitis
- **Exclusion:** Prior abdominal EBRT, prior invasive malignancy within 2 years, inability to target tumor or achieve dose constraints
- **Technique:**  $\geq 1$  gold fiducials required, 3-4 fractions delivered with Cyberknife platform
- **Primary outcome:** Local control
- **Secondary outcome:** Adverse events, quality of life

# Ongoing Phase II Clinical Trials

## [NCT02613819](#): Focal Ablative Stereotactic Radiosurgery for Cancers of the Kidney (FASTRACK II)

- **Estimated enrollment:** 70 patients
- **Inclusion:** Biopsy proven renal cancer in high-risk, medically inoperable patients or those who decline surgery
- **Exclusion:** Tumors > 8 cm, high-dose radiation to overlapping region, < 30 mLs/min GFR, recent cytotoxic chemotherapy, no concurrent chemo or targeted agents
- **Technique:** ≤ 4 cm size 26 Gy in 1 fraction, > 4 cm 42 Gy in 3 fractions
- **Primary outcome:** 1-year local progression
- **Secondary outcomes:** Tolerability, survival, distant failure rate, renal function change

## [NCT03747133](#): SABR for Renal Tumors

- **Estimated enrollment:** 30 patients
- **Inclusion:** Solid kidney mass (primary RCC or metastasis) ≤ 6 cm, inoperable, high-risk or declined surgery
- **Exclusion:** ≥ 5 active metastases, prior abdominal XRT leading to excessive cumulative kidney dose, concurrent systemic therapy, ESRD, familial syndrome with renal cancer predisposition
- **Technique:** 27.5 – 40 Gy in 5 fractions
- **Primary outcome:** Renal impairment
- **Secondary outcome:** Local control, acute and late toxicity, CKD progression, QOL

# Ongoing Phase II Clinical Trials

## [NCT03108703](#): Assessment of QoL Outcomes with SBRT for RCC (AQuOS-RCC)

- **Estimated enrollment:** 30 patients
- **Inclusion:** Biopsy proven renal cancer, radiologic growth on surveillance in medically inoperable patients or those who decline surgery,  $\geq 2.5$  cm or recurrence after ablative therapy
- **Exclusion:** Prior abdominal radiation
- **Technique:** 35 – 40 Gy in 5 fractions
- **Primary outcome:** QoL up to 5-years
- **Secondary outcomes:** Oncologic outcomes, treatment-related toxicity, cost-effectiveness

# ARROCase: CT/MRI Simulation

- SBRT delivered using MRI linac
  - Note: Non-MRI based radiosurgery also appropriate
- Patient instructed to fast 3 hours prior to simulation to limit stomach OAR volume
- Full-body immobilization
  - Abdominal compression techniques may be desirable
- Positioned supine with arms above head
- Simulation scans:
  - Free breathing CT without contrast, 2 mm slices
    - Can use contrast if not MRI guided adaptive therapy and renal function WNL
  - End exhale CT, 2 mm slices
    - Can use bellows device with 4DCT for delineation of ITV if not MRI guided adaptive therapy
  - T1 MRI simulation scan

# ARROCase: Treatment Planning

## OAR Delineation

- Bilateral kidneys
- Stomach
- Bowel loops
- Bowel substructures based on target:
  - Duodenum
  - Jejunum/Ileum
  - Colon
- Pancreas
- Liver (more relevant for right kidney targets)
- Left renal artery & vein

**NOTE:** When using 4DCT, evaluate OAR motion to ensure no movement into tumor targets. Consider overlap planning structures or PRV structures to better optimize OAR dose.

# ARROCase: Dose Constraints (5 fraction SBRT)

OAR	Volume	Volume Max (Gy)	Max Dose (Gy) [point max, unless noted]	Endpoint ( $\geq$ Grade 3)
Stomach	< 5 cc	26.5 Gy	< 32 Gy	Ulceration/fistula
Duodenum*	< 5 cc	18.3 Gy	< 32 Gy	Ulcer, bleeding, perforation
Jejunum/Ileum* [UK protocols] <sup>22</sup>	< 5 – 10 cc	25 Gy	< 30 – 35 Gy [0.5 cc]	Enteritis/obstruction
Colon*	< 20 cc	28.5 Gy	< 38 Gy	Colitis/fistula
Renal cortex **	200 cc (min. spared)	< 17.5 Gy	-	Renal dysfunction
Solitary or 1 kidney mean > 10 Gy <sup>22</sup>	<10% optimal < 45% mandatory	V10 Gy	-	Renal dysfunction
Renal hilum & vascular trunk	< 15 cc	23 Gy	-	Malignant hypertension
Liver**	700 cc (min. spared)	< 21 Gy	-	Liver dysfunction
Spinal cord	< 0.35 cc	22 Gy	< 28 Gy [to 0.035 cc] <sup>23</sup> < 25.3 [point max] <sup>24</sup>	Myelitis

\*Avoid circumferential radiation

\*\*Or 1/3 of the native total organ volume (prior to resection or volume reducing disease), whichever is greater

**See Also:** Reference [25], Reference [26], Reference [27], and radoncreview.org -> Dose Constraints

# ARROCase: Target Delineation

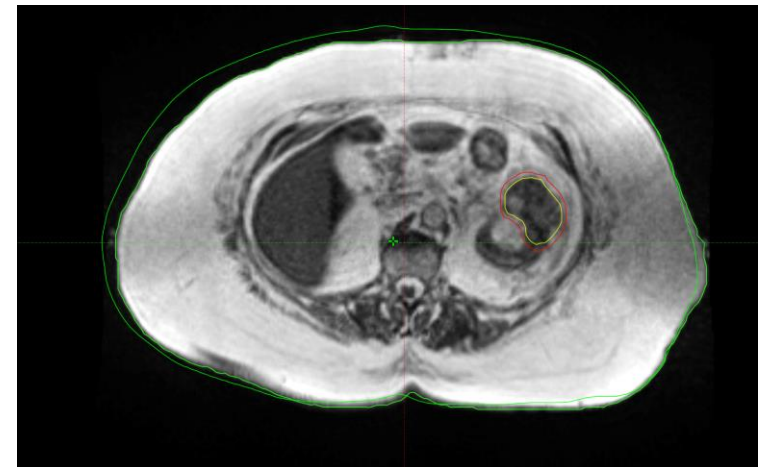
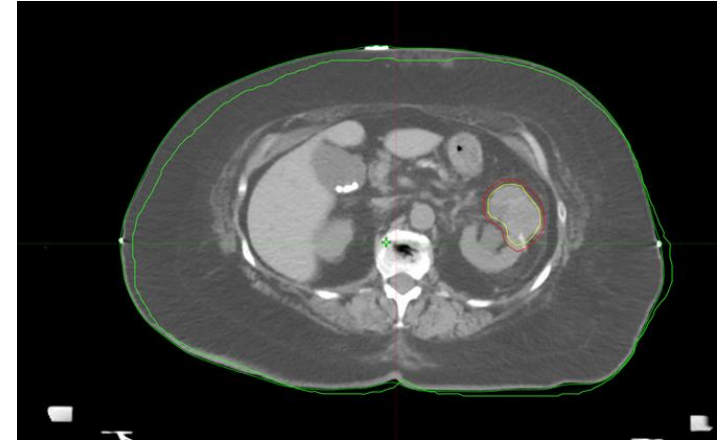
**Approach:** Dose paint PTV to 4000 cGy  
in 5 fractions with SIB to GTV of 5000  
cGy in 5 fractions

**GTV\_L\_Kidney\_5000 cGy**



**PTV\_L\_Kidney\_4000 cGy =**  
GTV\_L\_Kidney + 3 mm uniform  
expansion

**Note:** Delivered with a MRI linac  
using MRI guided adaptive  
replanning for each fraction, IMRT,  
and 12-fields



# ARROCase: OTVs and Follow-Up

- **OTVs:** Patient tolerated treatment with mild nausea and limited episode of diarrhea between 2<sup>nd</sup> and 3<sup>rd</sup> fraction.
- **Initial Follow-Up:** At initial follow-up, patient felt well with no side-effects of treatment noted. 9-month follow-up with stable disease and no evidence of metastases on serial imaging.



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