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

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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

• 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)
  – 8th 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

- **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)
- Alcohol
- Obesity
- Poorly-controlled hypertension
- **Kidney stones**
- **Occupational exposures**: benzene, vinyl chloride, coal tar, mineral oil, cadmium, herbicides, pesticides
- **Acetaminophen**
Genetic Syndromes

• **Von Hippel-Lindau syndrome**
  – Mutation in **VHL tumor suppressor gene**, inherited in an autosomal dominant pattern
  – **VHL regulates hypoxic inducible factor (HIF1α)**
  – 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

• **Tuberous sclerosis**
  – 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

Adrenal gland
Fibrous tissue (Gerota's fascia)
Fat layer
Kidney
Renal pelvis
Ureter

Anatomy

**Nephron**: functional unit of kidney

**Proximal tubule epithelium**:
- Clear cell RCC (75 – 80%)
- Papillary RCC (10 – 15%)

**Distal nephron/collecting tubule**:  
- Chromophobe RCC (5%)
- Collecting duct RCC (< 1%)

**Renal medullary carcinoma**:  
- Associated with sickle cell trait and hemoglobinopathies (rare)

Source: Anatomy & Physiology, Connexions Web site. [http://cnx.org/content/col11496/1.6/](http://cnx.org/content/col11496/1.6/), Jun 19, 2013
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Histology

Clear Cell Renal Cell Carcinoma\textsuperscript{11}
- 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\textsuperscript{12}
- Often circumscribed with pseudocapsule
- Papillae or tubulopapillary architecture with fibrovascular cores
- May contain foamy macrophages, psammoma bodies, hemosiderin

The Cancer Genome Atlas: Molecular Profiling

TCGA Pan-Kidney Cancer Analysis (n=843)

**Clear Cell RCC**
- Increased ribose metabolism pathway mRNA expression associated with poor survival
- Increased immune signature

**Chromophobe RCC**
- Identification of metabolically divergent (MD-) ChRCCs associated with extremely poor survival

**Type 1 Papillary RCC**
- *PBRM1* mutations associate with poor survival
- Increased mRNA signature for RNA splicing and cilia genes

**Type 2 Papillary RCC**
- Increased expression of the glycolysis, ribose metabolism, and Krebs cycle genes in comparison to Type 1 PRCC

**Renal Cell Carcinoma (RCC)**
- Increased DNA hypermethylation and CDKN2A alterations associate with poor prognosis in all RCC subtypes
- Increased Th2 immune signature within each RCC subtype associates with poor survival

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Graph showing survival rates for different types of RCC.

- ChRCC
- PRCC1
- PRCC2
- CCRCC
- RCC-CIMP

Survival rates for:
- CCRCC vs RCC-CIMP: p<0.0001
- CCRCC vs ChRCC: p=0.0008
- PRCC1 vs PRCC2: p=0.0478
- PRCC1 vs ChRCC: p=0.9138 N.S.
- PRCC2 vs RCC-CIMP: p<0.0001
Clinical Presentation

• **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

- 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$^{9,14}$

- **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)
<table>
<thead>
<tr>
<th><strong>CT</strong></th>
<th><strong>MRI</strong></th>
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<tbody>
<tr>
<td>Small lesions may enhance homogenously</td>
<td>T1 heterogeneous</td>
</tr>
<tr>
<td>Larger lesions may have irregular enhancement due to areas of necrosis</td>
<td>– Blood, necrosis, solid components</td>
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<tr>
<td>30% with calcification</td>
<td>T2 depends on histology</td>
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<tr>
<td>5-15% intraluminal growth into renal vein</td>
<td>– ccRCC: hyperintense</td>
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<tr>
<td>Prognosis worse for IVC involvement</td>
<td>– Papillary RCC: hypointense</td>
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<td></td>
<td>T1 contrast (Gd): arterial enhancement</td>
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<td></td>
<td>Distinguishes between bland and tumor thrombus in vessels</td>
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<tr>
<td>Prognostic Factors</td>
<td>Prognostic Risk Groups</td>
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<tr>
<td>-------------------</td>
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</tr>
<tr>
<td>1. &lt; 1 year from diagnosis to systemic therapy</td>
<td>• Favorable = 0 risk factors</td>
</tr>
<tr>
<td>2. PS &lt; 80% (Karnofsky)</td>
<td>• Intermediate = 1 – 2 risk factors</td>
</tr>
<tr>
<td>3. Hgb &lt; lower limit normal (12 g/dL)</td>
<td>• Poor = 3 – 6 risk factors</td>
</tr>
<tr>
<td>4. Ca$^{2+}$ &gt; ULN (10.2 mg/dL)</td>
<td></td>
</tr>
<tr>
<td>5. Neutrophil &gt; ULN (7x10$^9$/L)</td>
<td></td>
</tr>
<tr>
<td>6. Platelets &gt; ULN (400,000)</td>
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</table>
**AJCC 8th 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

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Treatment Options

• **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

- 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

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)\textsuperscript{17}

**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\textsuperscript{18}

• Feasible and safe for treatment of solitary kidney tumors\textsuperscript{19}

• 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
  - 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

Mayo Clinic RCC Tumor Thrombus Classification

<table>
<thead>
<tr>
<th>Level</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Limited to renal vein or its tributaries</td>
</tr>
<tr>
<td>1</td>
<td>Extends into IVC &lt; 2 cm above renal vein orifice</td>
</tr>
<tr>
<td>2</td>
<td>Extends into IVC &gt; 2 cm above renal vein orifice, but below hepatic veins</td>
</tr>
<tr>
<td>3</td>
<td>Extends above hepatic veins but below diaphragm</td>
</tr>
<tr>
<td>4</td>
<td>Extends above diaphragm</td>
</tr>
</tbody>
</table>

Source: Ramazan et al.²¹
Ongoing Phase II Clinical Trials

**NCT02141919**: SABR for Patients with Primary Renal Cancer
- **Estimated enrollment**: 16 patients
- **Inclusion**: Biopsy proven renal cancer ≤ 5 cm with growth ≥ 2 mm in a 1-year period
- **Exclusion**: No prior abdominal radiation, RFA, cryoablation or evidence of metastatic disease for ≥ 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 ≤ 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 constrains
- **Technique**: ≥ 1 gold fiducials required, 3-4 fractions delivered with Cyberknife platform
- **Primary outcome**: Local control
- **Secondary outcome**: Adverse events, quality of life

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### 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, ≥ 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

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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.

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### ARROCase: Dose Constraints (5 fraction SBRT)

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

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

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\textsuperscript{nd} and 3\textsuperscript{rd} 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.
References


References


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References


