Renal Cell Carcinoma

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Note: Consider Clinical Trials as treatment options for eligible patients.

Patients with renal cell carcinoma (RCC) diagnosed before age 46, regardless of histology, should be referred for genetic counseling and consideration of hereditary RCC syndromes.

INITIAL EVALUATION

Renal mass (excluding Wilms tumor)

- Chest x-ray or CT chest
- CT abdomen and optional CT pelvis
- MRI abdomen, if iodinated IV contrast not possible
- CBC with differential, sodium, potassium, carbon dioxide, BUN, creatinine, alkaline phosphatase, calcium, albumin
- Lifestyle risk assessment

Potential metastatic lesion identified?

- Yes
  - See metastatic disease on Page 4
- No
  - See multifocal renal masses on Page 3

Increased alkaline phosphatase or symptoms of bone pain?

- Yes
  - Bone scan and plain films of any symptomatic or suspicious areas
  - Lesion identified?
    - Yes
      - Further imaging as needed
      - Consider biopsy of lesion
    - No
      - See metastatic disease on Page 4
  - No
    - See Page 2
- No
  - Mass in contralateral kidney (multifocal disease, ipsilateral and/or contralateral)?
    - Yes
      - See Urothelial Carcinoma of Bladder and Upper Tract algorithm
    - No
      - Biopsy
      - Urine cytology
      - Impaired renal function or morphologically abnormal contralateral kidney?
        - Yes
          - Split renal function test
          - 24 hour urine for creatinine clearance
          - Consider Nephrology consult
        - No
          - See Page 2

Clinical suspicion of urothelial carcinoma?

- Yes
  - See Urothelial Carcinoma of Bladder and Upper Tract algorithm
- No
  - See Page 2

\(^1\) See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice

\(^2\) Retroperitoneal lymph nodes up to 3 cm do not imply unresectable disease. Lymph node biopsy not indicated.

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Renal Cell Carcinoma

Special anatomic considerations (e.g., inferior vena cava thrombus above hepatic vein or invasion of adjacent organs)?

- Yes
  - Special imaging
  - Additional surgical consult
  - Patient able to undergo resection?
    - Yes
      - Pathology report consistent with high risk of relapse?
        - Yes
          - Individualized decision regarding systemic treatment or observation
        - No
          - Observation
    - No
      - Complete resection?
        - Yes
          - Individualized decision regarding systemic treatment or observation
        - No
          - Possible embolization

- No
  - Partial nephrectomy
  - Radical nephrectomy
  - Minimally-invasive approach to radical or partial nephrectomy
  - Energy ablative technique [radio-frequency ablation (RFA), cryotherapy]
  - Watchful waiting or active surveillance, see Page 7

Note: Consider Clinical Trials as treatment options for eligible patients.
Renal Cell Carcinoma

Note: Consider Clinical Trials as treatment options for eligible patients.

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Multifocal renal masses

Complete staging:
- CT chest, abdomen and pelvis
- MRI brain (if signs or symptoms are present)
- Bone scan (if signs or symptoms are present)
- CBC with differential, sodium, potassium, chloride, carbon dioxide, BUN, creatinine, alkaline phosphatase, calcium, albumin
- Split renal function test

Clinical evidence and/or family history of hereditary renal cell carcinoma syndrome?

Refer to Genitourinary Genetics clinic at MD Anderson

Metastasis identified?

See metastatic disease on Page 4

Unilateral lesion

Nephron-sparing approaches or nephrectomy depending on anatomy

Bilateral lesion

Lesions amenable to nephron-sparing approaches?

Nephron-sparing approaches

Individualized decision regarding bilateral nephrectomy, systemic treatment, or observation

Note:

Evidence of von Hippel-Lindau disease includes:
- Retinal hemangiomas
- Cerebellar hemangioblastomas
- Spinal hemangioblastomas
- Renal cell carcinoma
- Pheochromocytoma
- Pancreatic cysts
- Pancreatic neuroendocrine tumors
- Endolymphatic sac tumors
- Round ligament cysts (females)
- Epididymal cysts (males)
Renal Cell Carcinoma

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Note: Consider Clinical Trials as treatment options for eligible patients.

CLINICAL PRESENTATION

METASTASES AT PRESENTATION OR RECURRENCE

Suspicion of metastatic disease

Staging:
- CT chest, abdomen, and pelvis
- CBC with differential, sodium, potassium, chloride, carbon dioxide, BUN, creatinine, LDH, alkaline phosphatase, calcium, albumin, AST
- MRI brain if clinically indicated
- Bone scan if clinically indicated

Anatomically threatening (e.g., brain lesion, imminent pathologic fracture, or biliary obstruction)?

Consider appropriate consultations:
- Surgery
- Radiation therapy
- Energy ablation
- Embolization

Consider cytoreductive nephrectomy if primary tumor in place, after appropriate multidisciplinary discussion
- Biopsy if not surgical candidate

Refer to systemic regimens on Page 5

If primary in place, consider cytoreductive nephrectomy, after appropriate multidisciplinary discussion

Surgically NED?

Resect metastasis
- If primary in place, consider cytoreductive nephrectomy, after appropriate multidisciplinary discussion

Observation versus pseudoadjuvant therapy in setting of clinical trial

NED = no evidence of disease

CLINICAL PRESENTATION

Yes

No

Multiple metastases

Solitary metastasis

Surgically resectable?

Consider local control modalities:
- Surgery
- Radiation therapy
- Energy ablation
- Embolization

Refer to systemic regimens on Page 5

Yes

No

Surgically NED?
Renal Cell Carcinoma

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PATHOLOGY

SYSTEMIC TREATMENT

- **Clear cell**
  - Clinical trial
  - Frontline agents – favorable-risk:
    - Axitinib plus pembrolizumab
    - Pazopanib
    - Sunitinib
  - Frontline agent – intermediate or poor risk:
    - Ipilimumab plus nivolumab
    - Axitinib plus pembrolizumab
    - Cabozantinib

- **Non-clear cell** (papillary, chromophobe, medullary, translocation carcinoma, collecting duct)
  - Clinical trial
  - Antiangiogenic agents: sunitinib, cabozantinib, axitinib, pazopanib, bevacizumab or
  - mTOR inhibitors: temsirolimus, everolimus or
  - Immunomodulatory agents: nivolumab plus ipilimumab or lenvatinib plus pembrolizumab or
  - Combination therapy: Levantanib plus everolimus, bevacizumab plus erlotinib (HLRCC related RCC), bevacizumab plus everolimus or
  - Carboplatin plus paclitaxel or gemcitabine plus doxorubicin (renal medullary carcinoma)
  - Consider empiric individualized therapy with available agents

- **Second-line agents:**
  - Nivolumab
  - Cabozantinib
  - Ipilimumab plus nivolumab
  - Lenvatinib plus everolimus
  - Axitinib
  - Axitinib plus pembrolizumab
  - Everolimus
  - Pazopanib
  - Sunitinib
  - Previously unused frontline agent

- **Prolonged period of stabilization and/or regression of lesions?**
  - Yes
    - Consider surgical consolidation or
    - Observation or
    - Change therapy
  - No
    - Change therapy

- **Response?**
  - Yes
    - Continue treatment to maximum response
    - Consider surgical consolidation or
    - Observation or
    - Change therapy
  - No
    - Change therapy

1. See Appendix A for drug dosing and schedule
2. International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria:
   - Good risk: meets none of the features below
   - Intermediate risk: meets 1-2 features below
   - Poor risk: meets 3 or more features below
   Features include:
   - Time from diagnosis to treatment < 1 year
   - Karnofsky Performance Status < 80%
   - Hypercalcemia (total calcium corrected for albumin)
   - Anemia
   - Neutrophilia
   - Thrombocytosis

HLRCC = hereditary leiomyomatosis and renal cell cancer

Note: Consider Clinical Trials as treatment options for eligible patients.
Renal Cell Carcinoma

**Evaluation**

**Clinical Stage I**
- T1a/T1b ≤ 7 cm
- Good surgical candidate?
  - Yes: Consider biopsy if atypical radiographic findings
  - No: Consider biopsy

**Clinical Stage II**
- > 7 cm
- Good surgical candidate?
  - Yes: Consider biopsy if atypical radiographic findings
  - No: Consider biopsy

**Clinical Stage III**
- T3a/T3b/N+
- Good surgical candidate?
  - Yes: Consider biopsy if atypical radiographic findings
  - No: Consider biopsy

**Clinical Stage IV**
- M+
- Good surgical candidate?
  - Yes: Medical oncology consult
  - No: Consider biopsy

**Systemic Therapy**
- See Page 5

**Embolization**
- Consider embolization to control primary if symptomatic

**Radical Nephrectomy**
- Partial nephrectomy (if anatomically feasible)
- Radical nephrectomy
- Energy ablation
- Active surveillance

**Active Surveillance**
- Systemic therapy
- Partial nephrectomy (if anatomically feasible)
- Radical nephrectomy
- Active surveillance
- Embolization

**Clinical Trial**
- Clinical trial for adjuvant treatment
- Systemic therapy (see Page 5) or Clinical trial

**Note:** Consider Clinical Trials as treatment options for eligible patients.

**Summary by Stage**

**Clinical Stage IV**
- M+
- Good surgical candidate?
  - Yes: Medical oncology consult
  - No: Consider biopsy

**Clinical Stage III**
- T3a/T3b/N+
- Good surgical candidate?
  - Yes: Consider biopsy if atypical radiographic findings
  - No: Consider biopsy

**Clinical Stage II**
- > 7 cm
- Good surgical candidate?
  - Yes: Consider biopsy if atypical radiographic findings
  - No: Consider biopsy

**Clinical Stage I**
- T1a/T1b ≤ 7 cm
- Good surgical candidate?
  - Yes: Consider biopsy if atypical radiographic findings
  - No: Consider biopsy

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SURVEILLANCE

**LOW RISK: T1a, T1b G1-2**

<table>
<thead>
<tr>
<th>Examination</th>
<th>Months</th>
<th>3</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
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<td>X</td>
<td>X</td>
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<td>O</td>
<td>O</td>
<td>O</td>
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<td>-</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Blood tests (^2)</td>
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<td>-</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

O = optional CT, abdominal MRI or abdominal US (ultrasound)

**INTERMEDIATE RISK: T1b G3-4, T2**

<table>
<thead>
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<th>Examination</th>
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<th>18</th>
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<tr>
<td>Blood tests(^2)</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

At 5 years and later: imaging every 1-2 years (abdominal imaging\(^1\) and either CT chest or chest x-ray)

**HIGH RISK: T3abc**

Follow up with history, physical exam, abdominal imaging\(^1\), CT chest, and blood tests\(^2\) at 6 weeks\(^3\), then every 6 months for the 1\(^{st}\) and 2\(^{nd}\) year, then every year afterwards. At 5 years and later: follow-up every 1-2 years with imaging (abdominal imaging\(^1\) and either CT chest or chest x-ray).

**VERY HIGH RISK: T4, any N+, any sarcomatoid or rhabdoid component**

Follow up with history, physical exam, abdominal imaging\(^1\), CT chest, and blood tests\(^2\) at 6 weeks\(^3\), then every 3 months in the 1\(^{st}\) year, then every 4 months in the 2\(^{nd}\) year, then every 6 months in the 3\(^{rd}\) and 4\(^{th}\) year. At 5 years and later: follow-up every 1-2 years with imaging (abdominal imaging\(^1\) and either CT chest or chest x-ray).

\(^1\) Abdominal imaging can be either MRI or CT with IV contrast
\(^2\) Blood tests include CBC, calcium, liver function tests, and alkaline phosphatase
\(^3\) Imaging may not be necessary at 6 weeks on M0 patients with negative imaging within weeks prior to surgery
APPENDIX A: Drug Dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Line</th>
<th>Dose and Schedule</th>
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</thead>
<tbody>
<tr>
<td>Pembrolizumab plus axitinib</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>● Pembrolizumab 200 mg IV every 3 weeks or 400 mg IV every 6 weeks;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Axitinib 5 mg PO twice daily</td>
</tr>
<tr>
<td>Nivolumab plus ipilimumab</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>● Nivolumab 3 mg/kg IV every 3 weeks for 4 doses, then 480 mg IV every 4 weeks;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Ipilimumab 1 mg/kg IV every 3 weeks for 4 doses</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>60 mg PO daily</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>50 mg 4 weeks on/2 weeks off or 2 weeks on/1 week off</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>800 mg PO daily</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; and later</td>
<td>60 mg PO daily</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; and later</td>
<td>480 mg IV every 4 weeks</td>
</tr>
<tr>
<td>Lenvatinib plus everolimus</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; and later</td>
<td>● Lenvatinib 18 mg PO daily;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Everolimus 5 mg PO daily</td>
</tr>
<tr>
<td>Axitinib</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; and later</td>
<td>5 mg PO twice daily</td>
</tr>
<tr>
<td>Everolimus</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; and later</td>
<td>10 mg PO daily</td>
</tr>
</tbody>
</table>
SUGGESTED READINGS


Renal Cell Carcinoma

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DEVELOPMENT CREDITS

This practice algorithm is based on majority expert opinion of the Genitourinary Center providers at the University of Texas MD Anderson Cancer Center. It was developed using a multidisciplinary approach that included input from the following:

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