Renal Cell Carcinoma

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, CMP, LDH, and UA
- Lifestyle risk assessment

Potential metastatic lesion identified?

Yes

- See metastatic disease on Page 4

No

- Increased alkaline phosphatase or symptoms of bone pain?

Yes

- Bone scan or bone survey and plain films of any symptomatic or suspicious areas

No

- Lesion identified?

Yes

- Further imaging as needed
- Consider biopsy of lesion

No

- See metastatic disease on Page 4

Mass in contralateral kidney (multifocal disease, ipsilateral and/or contralateral)?

Yes

- See multifocal renal masses on Page 3

No

Clinical suspicion of urothelial carcinoma?

Yes

- Biopsy
- Urine cytology

No

- Impaired renal function or morphologically abnormal contralateral kidney?

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.

CMP = comprehensive metabolic panel
LDH = lactate dehydrogenase
UA = urinalysis

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.
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 → Partial nephrectomy → Radical nephrectomy → Energy ablative technique (radio-frequency ablation (RFA), cryotherapy) → Active surveillance

No → Complete resection?

Yes → Individualized decision regarding systemic treatment or active surveillance

No → Possible embolization → Discuss Goal Concordant Care (GCC) with patient or if clinically indicated, with Patient Representative

Pathology report consistent with high risk of relapse?

Yes → Discuss adjuvant therapy or Surveillance

No → Surveillance

Individualized decision regarding systemic treatment or active surveillance

Discuss GCC with patient or if clinically indicated, with Patient Representative

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

1 GCC should be initiated by the Primary Oncologist. If Primary Oncologist is unavailable, Primary Team/Attending Physician to initiate GCC discussion and notify Primary Oncologist. Patients, or if clinically indicated, the Patient Representative should be informed of therapeutic and/or palliative options. GCC discussion should be consistent, timely, and re-evaluated as clinically indicated. The Advance Care Planning (ACP) note should be used to document GCC discussion. Refer to GCC home page (for internal use only).

2 For stage III clear cell carcinoma, consider clinical trial or adjuvant pembrolizumab up to a year.
Renal Cell Carcinoma

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

**Multifocal renal masses**

Complete staging:
- CT chest, abdomen and pelvis
- MRI brain (if signs or symptoms are present)
- Bone scan or bone survey (if signs or symptoms are present)
- CBC with differential, CMP, LDH, and UA
- Split renal function test

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

Metastasis identified?

- Yes
  - Refer to Genitourinary Genetics clinic at MD Anderson

- No
  - See metastatic disease on Page 4

Unilateral lesion

- Yes
  - Lesions amenable to nephron-sparing approaches?
    - Yes
      - Nephron-sparing approaches or nephrectomy depending on anatomy or
      - Active surveillance
    - No
      - Active surveillance

- No
  - Individualized decision regarding bilateral nephrectomy, systemic treatment, or active surveillance

Bilateral lesion

- Yes
  - Nephron-sparing approaches or nephrectomy depending on anatomy or
  - Active surveillance

- No
  - Nephrology consult

Features of von Hippel-Lindau disease includes:

- Major features:
  - Hemangioblastomas of the retina, spine, or brain
  - Clear Cell (cc) RCC diagnosed < 40 years of age or multiple/bilateral ccRCC tumors at any age
  - Pheochromocytoma
  - Paraganglioma of abdomen, thorax, or neck
  - Retinal angiomas

- Minor features:
  - Endolymphatic sac tumors
  - Papillary cystadenomas of the epididymis or broad ligament
  - Pancreatic serous cystadenoma (> 1)
  - Pancreatic neuroendocrine tumor or multiple pancreatic cysts (> 1)

Other hereditary RCC syndromes include:

- Hereditary Papillary Renal Carcinoma (HPRC) / MET gene
- Birt-Hogg-Dube syndrome (BDHS) / FLCN gene
- Tuberous Sclerosis Complex (TSC) / TSC1, TSC2 genes
- Hereditary Leiomyomatosis and RCC (HLRCC) / FH gene
- BAP1 Tumor Predisposition Syndrome (TPDS) / BAP1 gene
- Hereditary Paraganglioma / Pheochromocytoma (PCL/PCC) syndromes / SDHA/B/C/D genes

Department of Clinical Effectiveness V11
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Renal Cell Carcinoma

**CLINICAL PRESENTATION**

Suspicion of metastatic disease

**Staging:**
- CT chest, abdomen, and pelvis
- CBC with differential, CMP, LDH, and UA
- MRI brain if clinically indicated
- Bone scan or bone survey if clinically indicated

**A**

Multiple metastases

- Anatomically threatening (e.g., brain lesion, imminent pathologic fracture, or biliary obstruction)?
  - Yes
    - 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**
  - No
    - **Metastasis surgically resectable?**
      - Yes
        - **Resect metastasis**
        - If primary in place, consider cytoreductive nephrectomy, after appropriate multidisciplinary discussion
      - No

- **Solitary metastasis**
  - **Metastasis surgically resectable?**
    - Yes
      - **Surgically NED?**
        - Yes
          - **Discuss adjuvant therapy**
            - or
          - **Surveillance**
        - No
          - Refer to systemic regimens on Pages 5-6
    - No
      - Refer to systemic regimens on Pages 5-6

- **NED = no evidence of disease**

---

**METASTASES AT PRESENTATION OR RECURRENCE**

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

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

---

1 For stage M1 with NED after nephrectomy or resection of metastatic lesions, consider clinical trial or adjuvant pembrolizumab for up to a year
Renal Cell Carcinoma

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

PATHOLOGY

SYSTEMATIC TREATMENT

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)

Subsequent therapy agents:
- Preferred regimens
  - Cabozantinib
  - Lenvatinib plus everolimus
  - Nivolumab
- Other recommended regimens
  - Axitinib
  - Axitinib plus pembrolizumab
  - Cabozantinib plus nivolumab
  - Ipilimumab plus nivolumab
  - Lenvatinib plus pembrolizumab
  - Pazopanib
  - Sunitinib
  - High-dose interleukin-2

Useful in certain circumstances
- Active surveillance
- Axitinib
- Temozolomide
- Bevacizumab
- High-dose interleukin-2
- Temsirolimus

Frontline agents: Favorable risk
- Preferred regimens
  - Axitinib plus pembrolizumab
  - Cabozantinib plus nivolumab
  - Lenvatinib plus pembrolizumab
- Other recommended regimens
  - Axitinib plus avelumab
  - Cabozantinib
  - Ipilimumab plus nivolumab
  - Pazopanib
  - Sunitinib

Frontline agents: Intermediate or poor risk
- Preferred regimens
  - Axitinib plus pembrolizumab
  - Cabozantinib plus nivolumab
  - Ipilimumab plus nivolumab
  - Lenvatinib plus pembrolizumab
  - Cabozantinib
- Other recommended regimens
  - Axitinib plus avelumab
  - Pazopanib
  - Sunitinib

Useful in certain circumstances
- Everolimus
- Bevacizumab
- High-dose interleukin-2
- Sorafenib
- Temsirolimus
- Belzutifan

Clear cell

Prolonged period of stabilization and/or regression of lesions?
- Yes
  - Consider surgical consolidation or
  - Observation or
  - Change therapy
- No
  - Change therapy
  - Discuss GCC with patient or if clinically indicated, with Patient Representative

GCC should be initiated by the Primary Oncologist. If Primary Oncologist is unavailable, Primary Team/Attending Physician to initiate GCC discussion and notify Primary Oncologist. Patients, or if clinically indicated, the Patient Representative should be informed of therapeutic and/or palliative options. GCC discussion should be consistent, timely, and re-evaluated as clinically indicated. The Advance Care Planning (ACP) note should be used to document GCC discussion. Refer to GCC home page (for internal use only).

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Renal Cell Carcinoma

**PATHOLOGY**
- Non-clear cell (papillary, chromophobe, medullary, translocation carcinoma, collecting duct)

**SYSTEMIC TREATMENT**

- **Preferred:**
  - Clinical trial
  - Cabozantinib
  - Sunitinib

- **Other recommended regimens:**
  - Nivolumab
  - Pembrolizumab
  - Nivolumab plus cabozantinib

- **Useful in certain circumstances:**
  - Axitinib
  - Bevacizumab plus erlotinib
  - Bevacizumab (HLRCC related RCC and/or papillary RCC)
  - Everolimus
  - Pazopanib
  - Temsirolimus
  - Carboplatin plus paclitaxel or gemcitabine plus doxorubicin (renal medullary carcinoma)
  - Consider empiric individualized therapy with available agents

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

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

HLRCC = hereditary leiomyomatosis and renal cell cancer

1. See Appendix A for drug dosing and schedule
2. GCC should be initiated by the Primary Oncologist. If Primary Oncologist is unavailable, Primary Team/Attending Physician to initiate GCC discussion and notify Primary Oncologist. Patients, or if clinically indicated, the Patient Representative should be informed of therapeutic and/or palliative options. GCC discussion should be consistent, timely, and re-evaluated as clinically indicated. The Advance Care Planning (ACP) note should be used to document GCC discussion. Refer to GCC home page (for internal use only).
Renal Cell Carcinoma

EVALUATION

SUMMARY BY STAGE

Clinical Stage I
T1a/T1b ≤ 7 cm

- Chest x-ray or CT chest
- CT abdomen and optional CT pelvis
- MRI abdomen
- CBC with differential and CMP
- MRI/CT brain if clinically indicated
- Central nervous system imaging if clinically indicated

Clinical Stage II
> 7 cm

Clinical Stage III
T3a/T3b/N+

Clinical Stage IV
M+

Good surgical candidate?

Yes → Consider biopsy if atypical radiographic findings

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

No → Consider biopsy

- Energy ablation
- Active surveillance

Yes → Consider biopsy if atypical radiographic findings

- Partial nephrectomy (if anatomically feasible)
- Radical nephrectomy

No → Consider biopsy

- Active surveillance
- Embolization

Yes → Consider biopsy if atypical radiographic findings

- Radical nephrectomy
- Partial nephrectomy (optional)

No → Consider biopsy

- Systemic therapy
- Active surveillance
- Embolization

Yes → Medical oncology consult

Consider cytoreductive nephrectomy, after appropriate multidisciplinary discussion (and resection of single metastasis if possible)

No → Consider medical oncology consult

Consider embolization to control primary if symptomatic

- Systemic therapy (see Pages 5-6)

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

1 For stage II clear cell carcinoma, consider clinical trial or adjuvant pembrolizumab (grade 4 tumors with clear cell histology with or without sarcomatoid features) for up to a year

2 For stage III clear cell carcinoma, consider clinical trial or adjuvant pembrolizumab (preferred) or sunitinib for up to a year

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SURVEILLANCE

Risk Classification

If final microscopic surgical margins are positive for cancer, the risk category should be considered at least one level higher, and increased clinical vigilance should be exercised.

<table>
<thead>
<tr>
<th>Risk Classification</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>48</th>
<th>60</th>
<th>72-84</th>
<th>96-120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk (LR): pT1 and Grade 1/2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>X</td>
<td>-</td>
<td>X</td>
<td>-</td>
<td>-</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Intermediate Risk (IR): pT1 and Grade 3/4, or pT2 any Grade</td>
<td>-</td>
<td>X</td>
<td>-</td>
<td>X</td>
<td>-</td>
<td>X</td>
<td>-</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>High Risk (HR): pT3 any Grade</td>
<td>-</td>
<td>X</td>
<td>-</td>
<td>X</td>
<td>-</td>
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<td>-</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Very High Risk (VHR): pT4 or pN1, or sarcomatoid/rhabdoid dedifferentiation, or macroscopic positive margin</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
</tr>
</tbody>
</table>

Recommended follow-up schedule after surgery for renal cancer (in months)¹

₁ Follow-up timeline is approximate and allows flexibility to accommodate reasonable patient, caregiver, and institutional needs. Each follow-up visit should include relevant history, physical examination, laboratory testing, and abdominal and chest imaging. Overall, 30% of renal cancer recurrences after surgery are diagnosed beyond 60 months. Informed/shared decision-making should guide surveillance decisions beyond 60 months.
### APPENDIX A: Drug Dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose and Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>200 mg IV every 3 weeks or 400 mg IV every 6 weeks</td>
</tr>
<tr>
<td>Axitinib plus pembrolizum</td>
<td>• Axitinib 5 mg PO twice daily</td>
</tr>
<tr>
<td></td>
<td>• Pembrolizumab 200 mg IV every 3 weeks or 400 mg IV every 6 weeks</td>
</tr>
<tr>
<td>Cabozantinib plus nivolumab</td>
<td>• Cabozantinib 40 mg PO daily</td>
</tr>
<tr>
<td></td>
<td>• Nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks</td>
</tr>
<tr>
<td>Lenvatinib plus pembrolizum</td>
<td>• Lenvatinib 20 mg PO daily</td>
</tr>
<tr>
<td></td>
<td>• Pembrolizumab 200 mg IV every 3 weeks or 400 mg IV every 6 weeks</td>
</tr>
<tr>
<td>Ipilimumab plus Nivolumab</td>
<td>• Ipilimumab 1 mg/kg IV every 3 weeks for 4 doses</td>
</tr>
<tr>
<td></td>
<td>• Nivolumab 3 mg/kg (maximum dose 240 mg) IV every 3 weeks for 4 doses, then 6 mg/kg (maximum dose 480 mg) IV every 4 weeks</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>60 mg PO daily</td>
</tr>
<tr>
<td>Lenvatinib plus everolimus</td>
<td>• Lenvatinib 18 mg PO daily</td>
</tr>
<tr>
<td></td>
<td>• Everolimus 5 mg PO daily</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>6 mg/kg (maximum dose 480 mg) IV every 4 weeks or 3 mg/kg (maximum dose 240 mg) IV every 2 weeks</td>
</tr>
<tr>
<td>Axitinib</td>
<td>5 mg PO twice daily</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>800 mg PO daily</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>50 mg PO daily for 4 weeks on/2 weeks off or 2 weeks on/1 week off</td>
</tr>
<tr>
<td>Axitinib plus avelumab</td>
<td>• Axitinib 5 mg PO twice daily</td>
</tr>
<tr>
<td></td>
<td>• Avelumab 800 mg IV every 2 weeks</td>
</tr>
<tr>
<td>Tivozanib</td>
<td>1.34 mg PO daily on days 1 to 21 of a 28-day cycle</td>
</tr>
<tr>
<td>Belzutifan</td>
<td>120 mg PO daily</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>10 mg/kg IV every 2 weeks (or 15 mg/kg IV every 3 weeks)</td>
</tr>
<tr>
<td>Everolimus</td>
<td>10 mg PO daily</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>25 mg IV weekly</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>400 mg PO twice daily</td>
</tr>
</tbody>
</table>
SUGGESTED READINGS


MD Anderson Institutional Policy #CLN1202 - Advance Care Planning Policy

Advance Care Planning (ACP) Conversation Workflow (ATT1925)

Continued on next page
Renal Cell Carcinoma

SUGGESTED READINGS - continued


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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