# Renal Cell Carcinoma

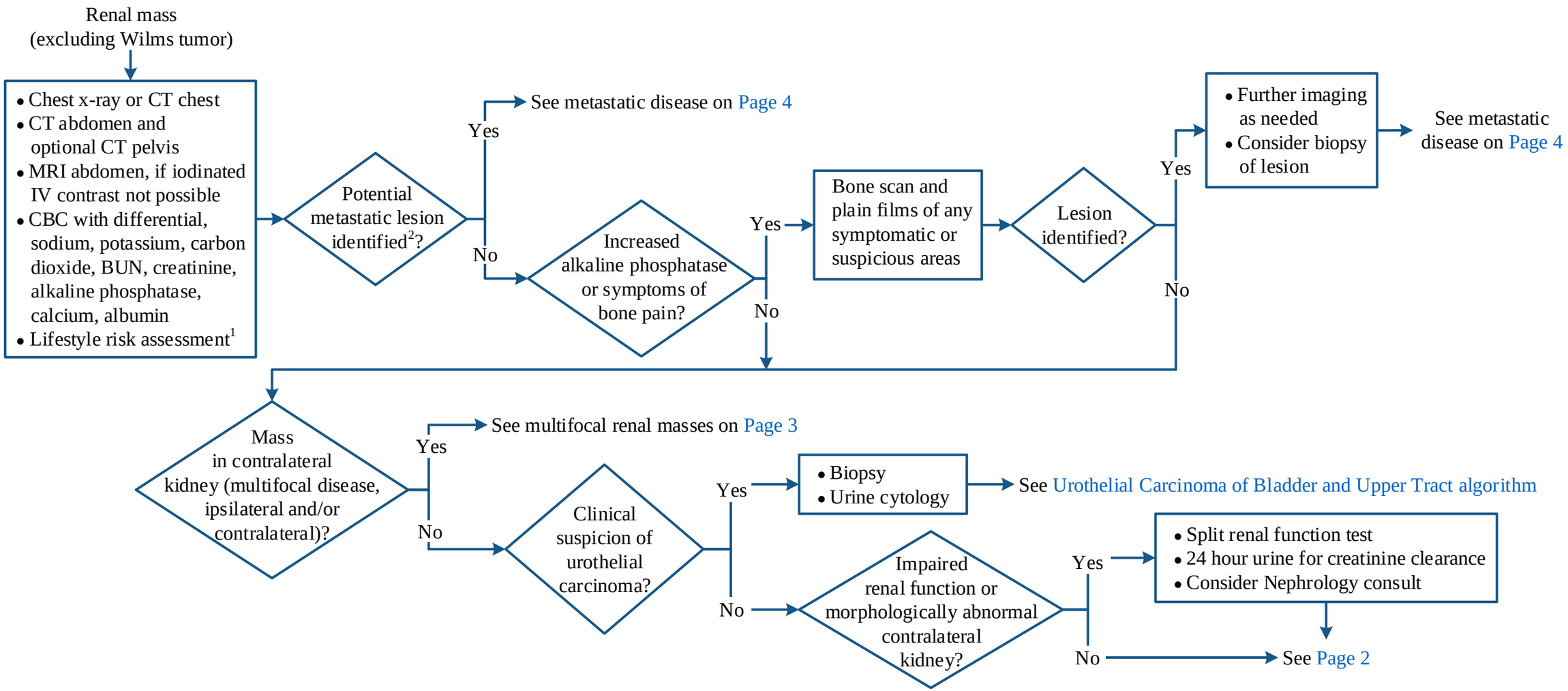




**Note:** Consider Clinical Trials as treatment options for eligible patients.

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




[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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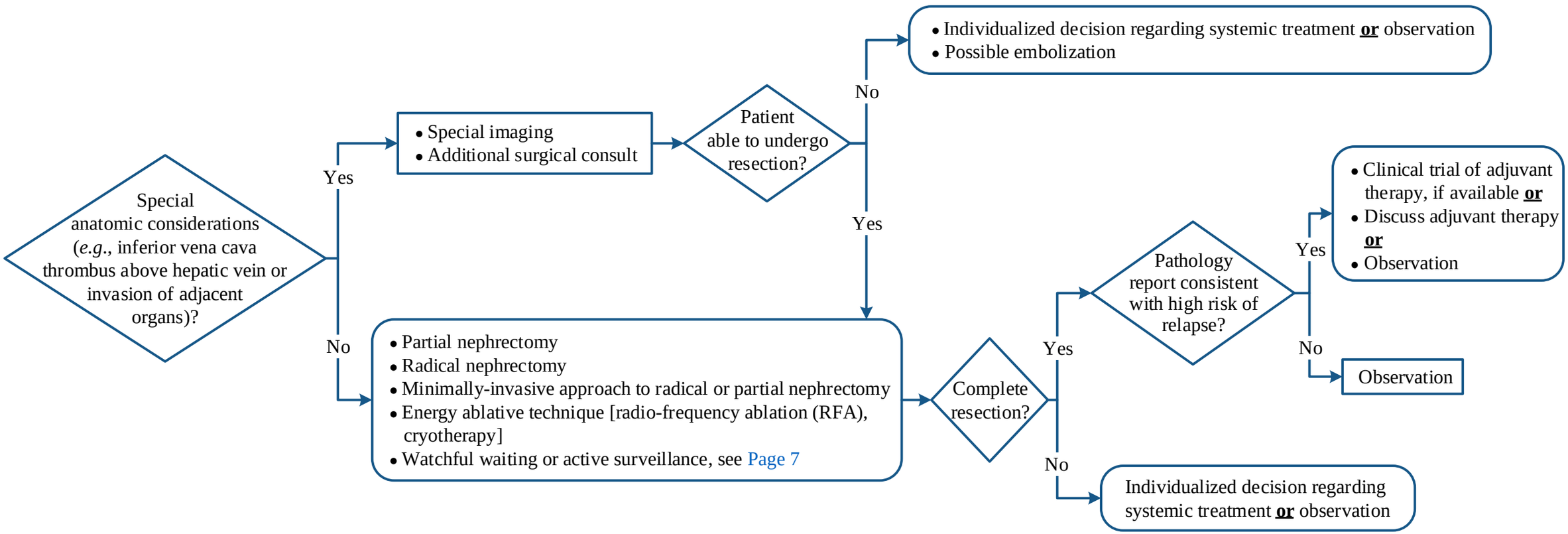

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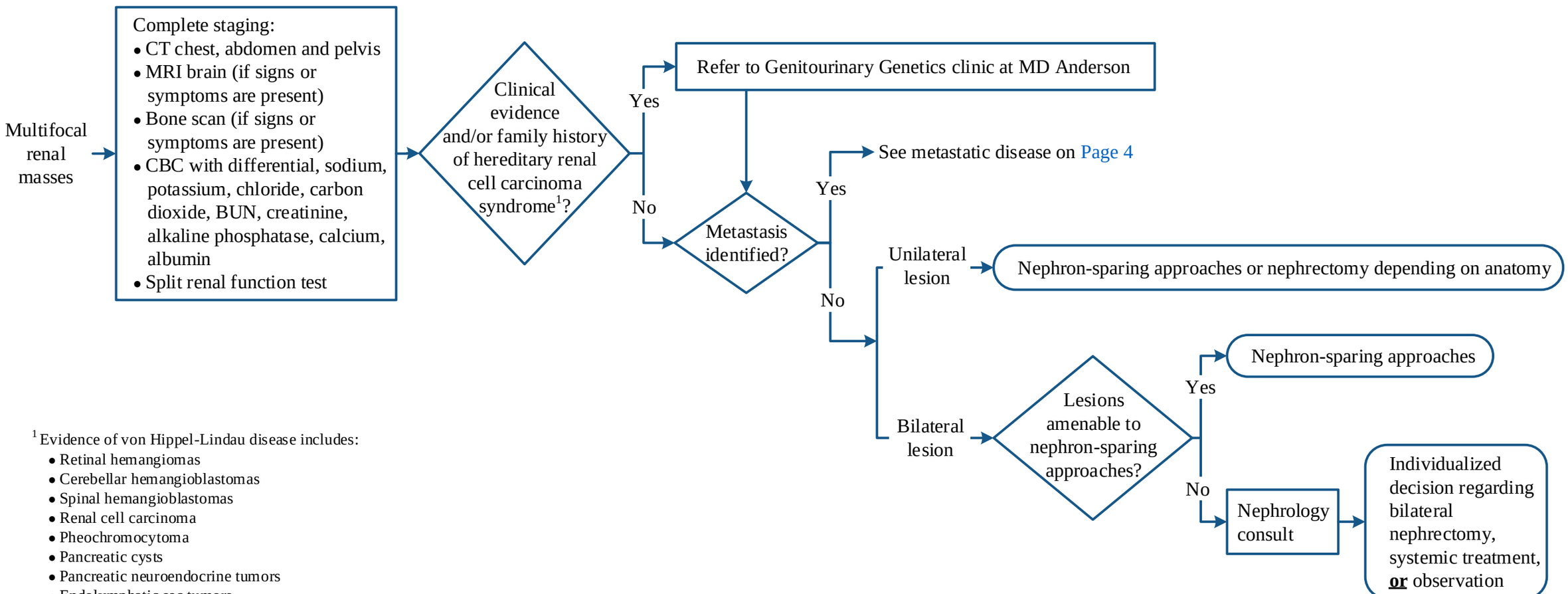


[1] Evidence of von Hippel-Lindau disease includes:
- Retinal hemangiomas
- Cerebellar hemangioblastomas
- Spinal hemangioblastomas
- Renal cell carcinoma
- Pheochromocytoma
- Pancreatic cysts
- Pancreatic neuroendocrine tumors
- Endolymphatic sac tumors
- Round ligament cysts (females)
- Epididymal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



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## CLINICAL PRESENTATION

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

**A**

Multiple metastases

Solitary metastasis

## METASTASES AT PRESENTATION OR RECURRENCE

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

Yes

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

No

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

Refer to systemic regimens on Page 5

Metastasis surgically resectable?

No

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

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

Yes

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

Surgically NED?

No

Refer to systemic regimens on Page 5

Yes

Observation versus pseudoadjuvant therapy in setting of clinical trial

NED = no evidence of disease

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**PATHOLOGY** **SYSTEMIC TREATMENT**[1]

Clear cell

- Clinical trial
- Frontline agents – favorable-risk[2]:
  - Axitinib plus pembrolizumab
  - Pazopanib
  - Sunitinib
- Frontline agent – intermediate or poor risk:
  - Ipilimumab plus nivolumab
  - Axitinib plus pembrolizumab
  - Cabozantinib
- 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

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

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



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## EVALUATION

- Chest x-ray or CT chest
- CT abdomen and optional CT pelvis
- MRI abdomen
- CBC with differential, sodium, potassium, carbon dioxide, BUN, creatinine, alkaline phosphatase, calcium, albumin
- MRI/CT brain if clinically indicated
- Central nervous system imaging if clinically indicated

## SUMMARY BY STAGE

### Clinical Stage I T1a/T1b ≤ 7 cm

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

### Clinical Stage II > 7 cm

Good surgical candidate?

- **Yes** → Consider biopsy if atypical radiographic findings
  - Partial nephrectomy (if anatomically feasible)
  - Radical nephrectomy
- **No** → Consider biopsy
  - Active surveillance
  - Embolization

### Clinical Stage III T3a/T3b/N+

Good surgical candidate?

- **Yes** → Consider biopsy if atypical radiographic findings
  - Radical nephrectomy
  - Partial nephrectomy (optional)
  - → Clinical trial for adjuvant treatment
- **No** → Consider biopsy
  - Systemic therapy
  - Active surveillance
  - Embolization

### Clinical Stage IV M+

Good surgical candidate?

- **Yes** → Medical oncology consult → Consider cytoreductive nephrectomy, after appropriate multidisciplinary discussion (and resection of single metastasis if possible)
  - Systemic therapy (see Page 5) **or**
  - Clinical trial
- **No** → Consider embolization to control primary if symptomatic → Systemic therapy (see Page 5)

# Renal Cell Carcinoma





## SURVEILLANCE

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

| | Months | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Examination | 3 | 6 | 12 | 18 | 24 | 30 | 36 | 48 | 60 |
| History | - | - | X | - | X | - | X | X | X |
| Physical exam | - | - | X | - | X | - | X | X | X |
| Abdominal imaging | - | - | X[1] | - | O | - | O | O | O |
| Chest x-ray | - | - | X | - | X | - | X | X | X |
| Blood tests[2] | - | - | X | - | X | - | X | X | X |

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

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

| | Months | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Examination | 3 | 6 | 12 | 18 | 24 | 30 | 36 | 48 | 60 |
| History | - | X | X | X | X | X | X | X | X |
| Physical exam | - | X | X | X | X | X | X | X | X |
| Abdominal imaging[1] | - | X | X | - | X | - | X | - | X |
| CT chest | - | X | X | - | X | - | X | X | X |
| Blood tests[2] | - | X | X | X | X | X | X | X | X |

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 1st and 2nd 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 1st year, then every 4 months in the 2nd year, then every 6 months in the 3rd and 4th 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

| Drug | Line | Dose and Schedule |
|---|---|---|
| Pembrolizumab plus axitinib | 1st | • Pembrolizumab 200 mg IV every 3 weeks or 400 mg IV every 6 weeks;<br>• Axitinib 5 mg PO twice daily |
| Nivolumab plus ipilimumab | 1st | • Nivolumab 3 mg/kg IV every 3 weeks for 4 doses, then 480 mg IV every 4 weeks;<br>• Ipilimumab 1 mg/kg IV every 3 weeks for 4 doses |
| Cabozantinib | 1st | 60 mg PO daily |
| Sunitinib | 1st | 50 mg 4 weeks on/2 weeks off **or** 2 weeks on/1 week off |
| Pazopanib | 1st | 800 mg PO daily |
| Cabozantinib | 2nd and later | 60 mg PO daily |
| Nivolumab | 2nd and later | 480 mg IV every 4 weeks |
| Lenvatinib plus everolimus | 2nd and later | • Lenvatinib 18 mg PO daily;<br>• Everolimus 5 mg PO daily |
| Axitinib | 2nd and later | 5 mg PO twice daily |
| Everolimus | 2nd and later | 10 mg PO daily |

## SUGGESTED READINGS

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## DEVELOPMENT CREDITS

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