# Benign and malignant renal tumors

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111/10

# Benign and malignant renal mass

**BOX 57-1** Renal Masses Classified by Pathologic Features

**MALIGNANT**
- Renal cell carcinoma
- Urothelium-based cancers
  - Urothelial carcinoma
  - Squamous cell carcinoma
  - Adenocarcinoma
- Sarcomas
  - Leiomyosarcoma
  - Liposarcoma
  - Angiosarcoma
  - Hemangiopericytoma
  - Malignant fibrous histiocytoma
  - Synovial sarcoma
  - Osteogenic sarcoma
  - Clear cell sarcoma
  - Rhabdomyosarcoma
- Wilms tumor
- Primitive neuroectodermal tumor
- Carcinoid tumor
- Lymphoma/leukemia
- Metastasis
- Invasion by adjacent neoplasm

**BENIGN**
- Cystic lesions
  - Simple cyst
  - Hemorrhagic cyst

**BENIGN—cont'd**
- Solid lesions
  - Angiomyolipoma
  - Oncocytoma
  - Renal adenoma
  - Metanephric adenoma
  - Cystic nephroma
  - Mixed epithelial-stromal tumor
  - Reninoma (juxtaglomerular cell tumor)
  - Leiomyoma
  - Fibroma
  - Hemangioma
- Vascular lesions
  - Renal artery aneurysm
  - Arteriovenous malformation
- Pseudotumor

**INFLAMMATORY**
- Abscess
- Focal pyelonephritis
- Xanthogranulomatous pyelonephritis
- Infected renal cyst
- Tuberculosis
- Rheumatic granuloma

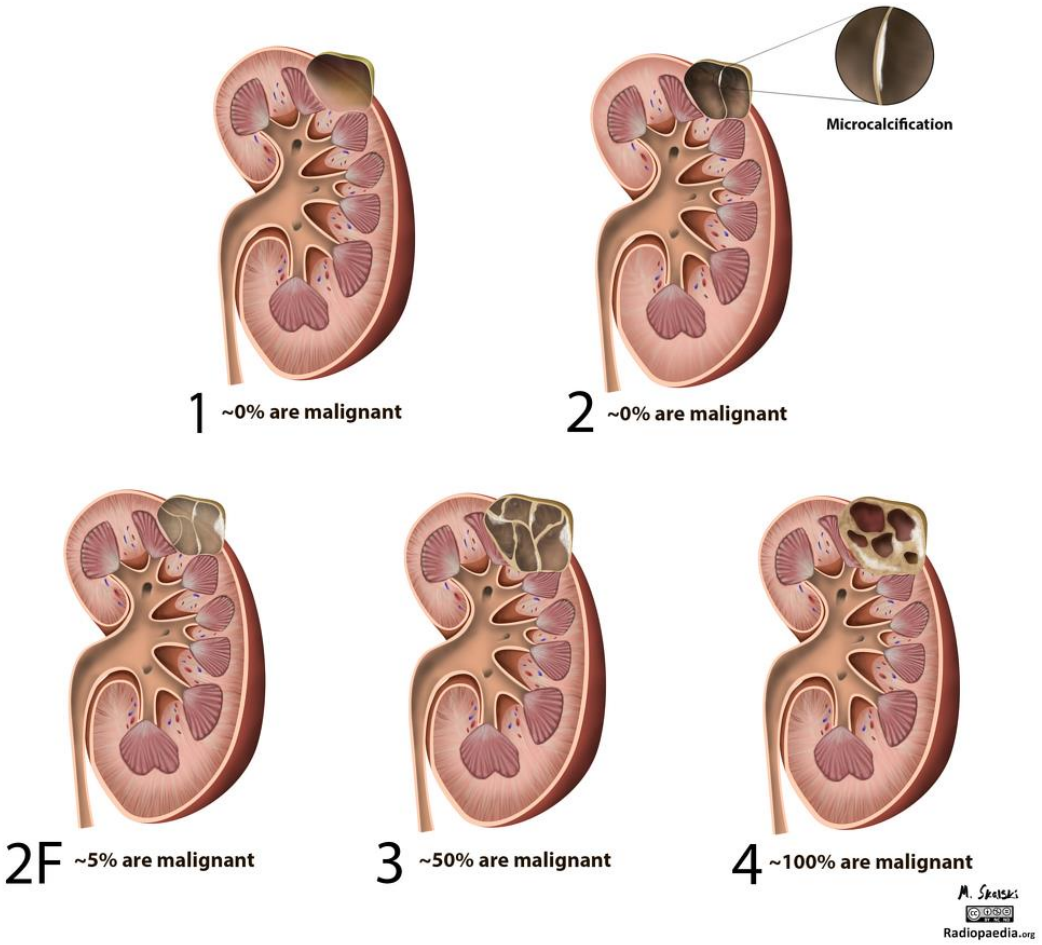
# Small renal mass (<4cm)

- Cystic renal mass
  - Simple cyst
  - Cystic RCC
- Solid renal mass
  - Angiomyolipoma (AML)
  - Oncocytoma
  - Pseudotumor
  - Renal cell carcinoma (RCC)
  - Urothelial carcinoma (UC)
  - Lymphoma
  - Sarcoma
  - Metastasis

CT with/without contrast

# Bosniak classification

## Bosniak classification of renal cysts




### Bosniak renal cyst classification

| Category | CT features | Significance |
|---|---|---|
| I | Thin wall, water density & does not enhanced<br>No septa, calcification, or solid component | Benign |
| II | Thin septa with "perceived" enhancement<br>Fine or slightly thick calcification<br>High attenuation non-enhancing cyst < 3 cm | Benign |
| IIF | Thick regular septa with "perceived" enhancement<br>Thick regular wall with "perceived" enhancement<br>Thick, nodular, & irregular calcification | Likely benign<br>Follow-up |
| III | Thick smooth or irregular septa<br>Thick smooth or irregular wall<br>With measurable enhancement | Some benign<br>Some malignant |
| IV | Criteria of category III<br>Enhancing mass independent of wall or septa | Malignant<br>Cystic carcinoma |

Israel GM & Bosniak MA. Urology 2005 ; 66 : 484 – 488.

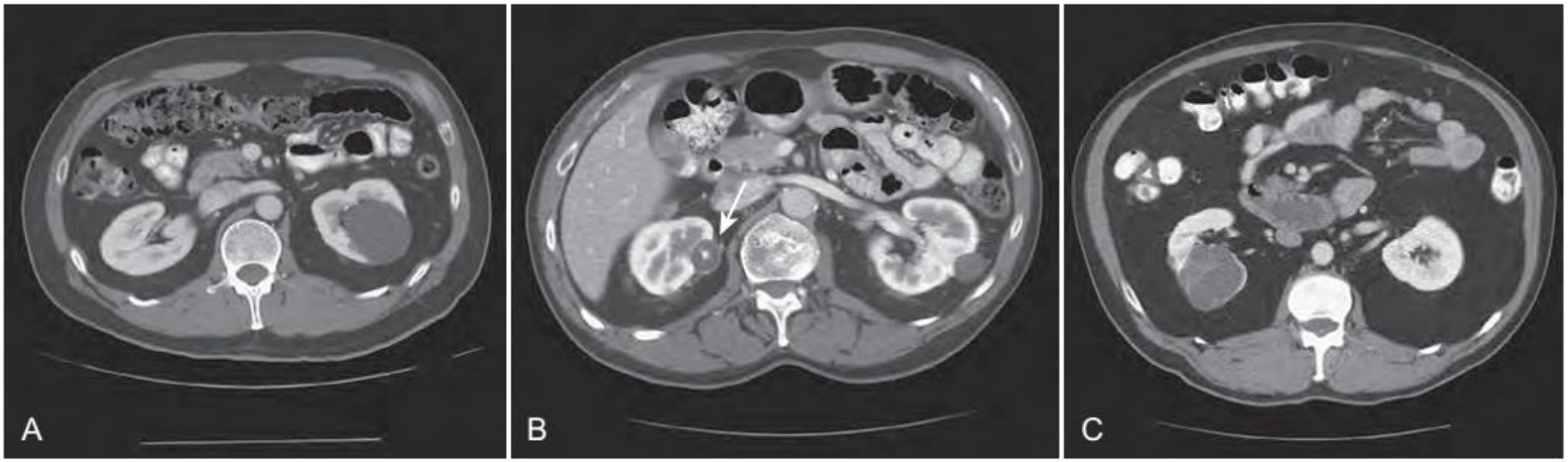



Figure 56-1. A, Computed tomography (CT) scan of a Bosniak I renal cyst. B, CT scan of a Bosniak II renal cyst. Note internal calcification. C, CT scan of a Bosniak IIF renal cyst. Several thin irregular septations are present within the cyst. (Copyright 2009, C. G. Wood.)

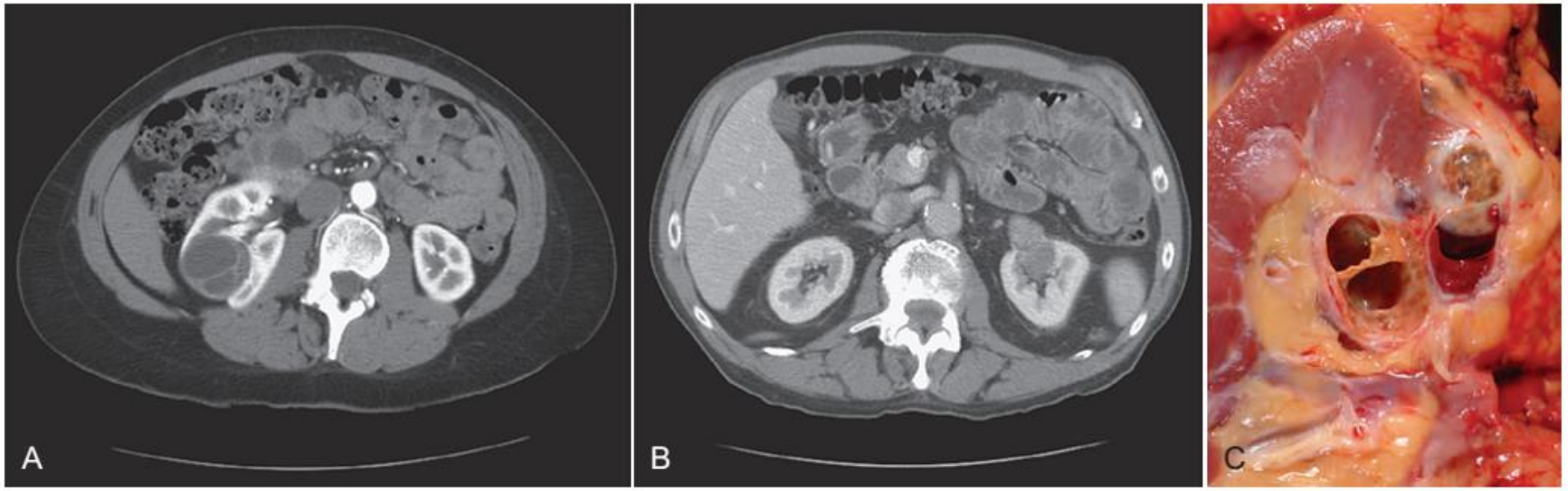



Figure 56-2. A, Computed tomography (CT) scan of a Bosniak III renal cyst. Thick, irregular septations are present within the cyst. B, CT scan of a Bosniak IV renal cyst, with a solid enhancing nodule. C, Bivalved Bosniak IV renal cyst demonstrating a solid component that proved to be conventional renal cell carcinoma. (Copyright 2009, C. G. Wood.)

# Abdominal CT for solid renal mass

| Differential Diagnosis | CT |
|---|---|
| RCC | Enhancing (>12-20 HU) mass with IV contrast, may have cystic component, calcifications (30%), hemorrhage or necrosis [13] |
| Transitional cell carcinoma | Often ill-defined mass located centrally; radiolucent filling defect, obstruction or nonvisualization of the collecting system with IV contrast [1] |
| Sarcoma | Soft tissue mass arising from capsule or renal sinus, often quite large without lymphadenopathy; presence of fat suggests liposarcoma [1] |
| Lymphoma | Multiple small renal masses (most common pattern), diffuse renal involvement, or direct invasion of lymphadenopathy into kidney. Usually hypoattenuating, occasionally hyperattenuating. [1] |
| Metastases | Multiple masses, moderate enhancement with IV contrast. [1] |
| Oncocytoma | Central stellate scar [1] |
| Angiomyolipoma | Heterogeneous mass with areas of negative attenuation (below -20 HU) without calcifications [1] |
| Pseudotumor | Renal segment that is isodense with surrounding parenchyma [1] |

**Table 2.** Differential diagnosis for solid renal mass

- In 10% to 20% of solid renal masses, CT findings are indeterminate
  - Poor enhanced RCC, fat-poor AML, oncocytoma…

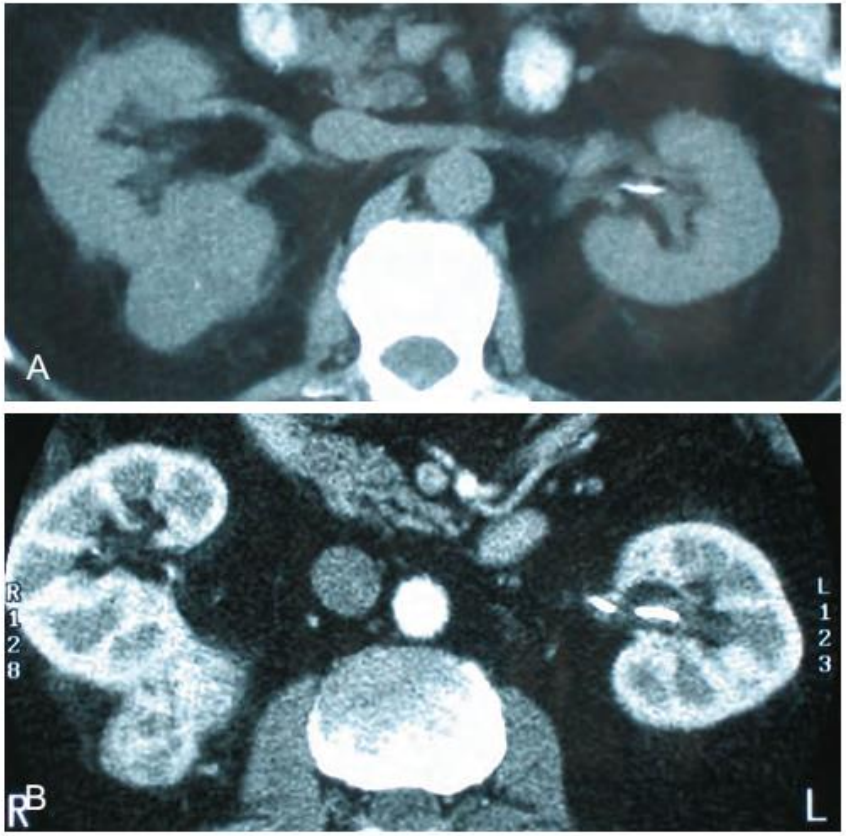



Figure 57-2. A, Computed tomography (CT) scan without administration of contrast material shows solid, right posterior renal mass. B, After administration of the contrast agent, CT scan shows that the mass enhances more than 20 HU and is thus highly suggestive of renal cell carcinoma (RCC). This mass was excised and confirmed to be a clear cell RCC. (Courtesy Dr. Terrence Demos, Maywood, IL.)

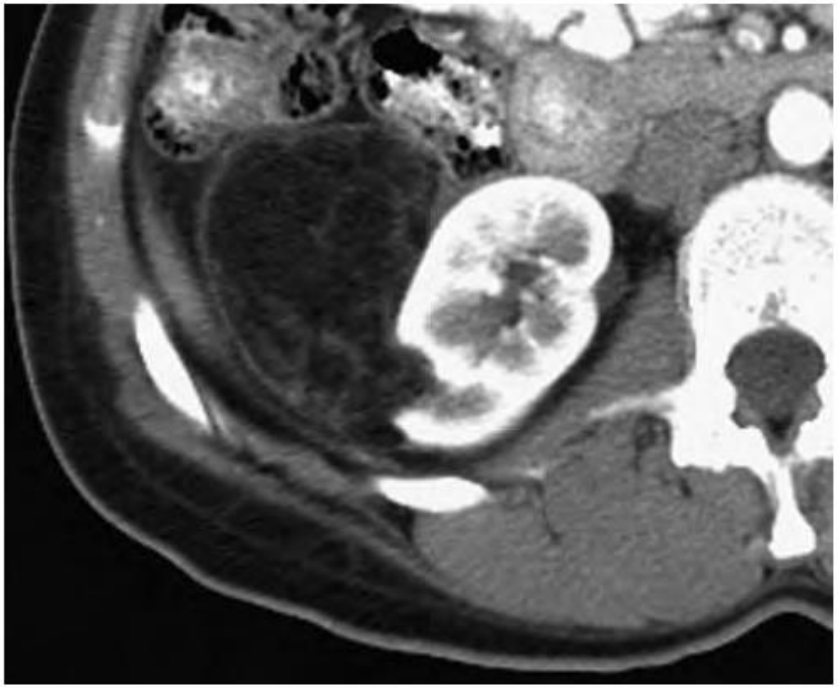


Figure 56-8. Computed tomography scan of angiomyolipoma with parenchymal indentation. (Copyright 2009, S. F. Matin.)

# Needle biopsy

- CT-guided core biopsy, minimal risk of bleeding and seeding of the needle tract
- In past, higher false negative rate (negative predictive value, 60%)

- Recent, sensitivity 99.7%, specificity 93.2%
- 10% of patients could avoid treatment with confirmed begin histology
- 10-20% non-diagnostic biopsy, repeat biopsy
- Indications:
  - should be performed when results might alter surgical management
  - Pre-thermal ablation

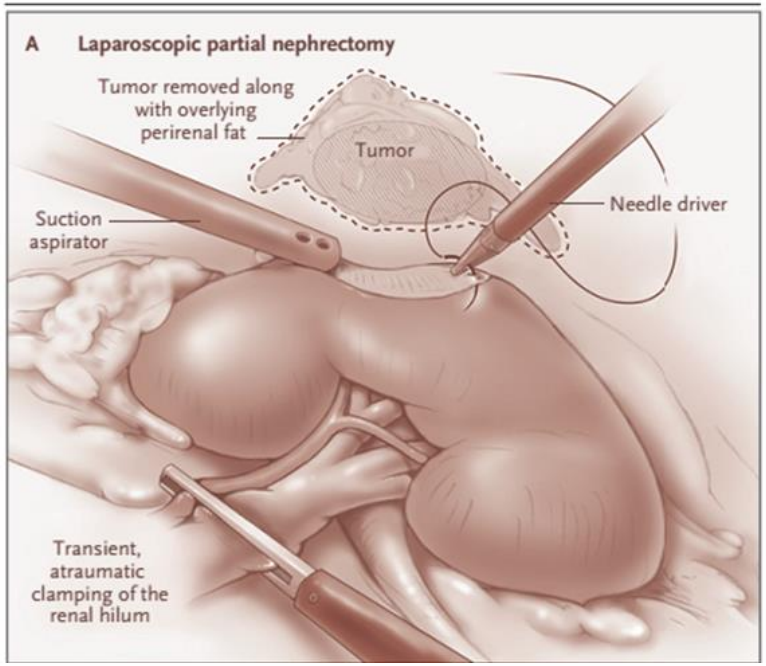
# Active surveillance

- Serial image for size every 6-12 months
- Most small RCC(<4cm) grows slowly 2-3mm/year, <5% metastatic rate in first 3 years, SRM<1cm are benign in 50% of cases

- Indications:
  - significant comorbidities
  - limited life expectancy(< 5-10years)
  - SRM <1cm

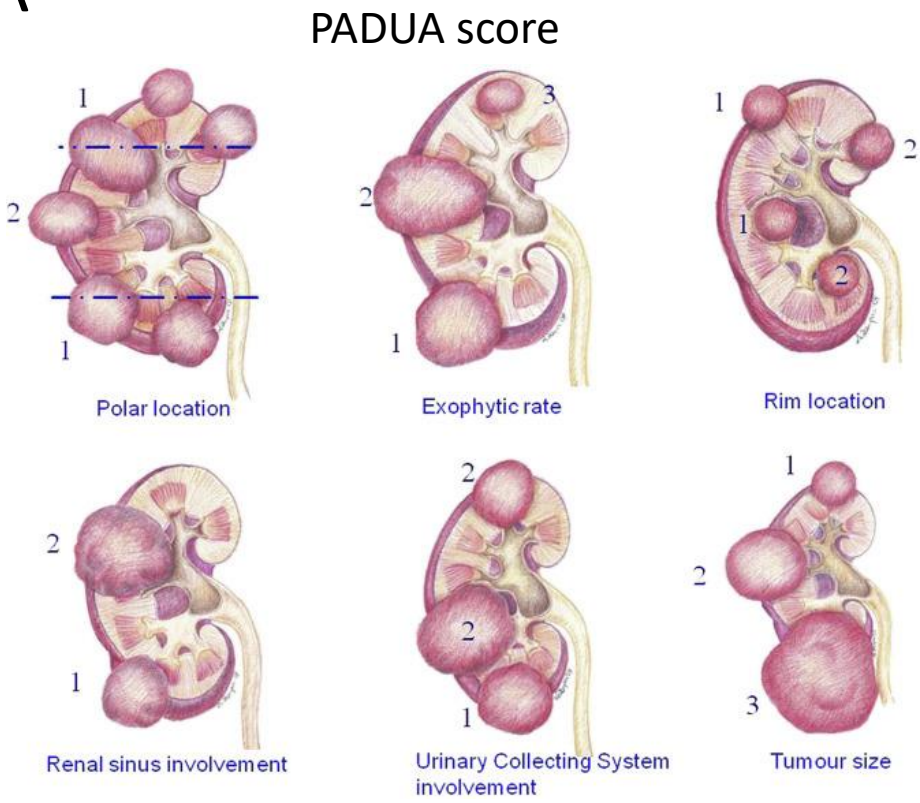
# Partial nephrectomy

- Partial nephrectomy (PN) for SRMs is the standard treatment.
- Slight higher complication(vs. radical)
  - severe hemorrhage(3.1% vs. 1.2%)
  - urine leak (4.4% vs. 0%)
  - reoperation (4.4% vs. 2.4%)
- the most durable follow-up data (up to 15 yr) concerning oncology and renal function
- laparoscopic, open surgical, or robotic approach



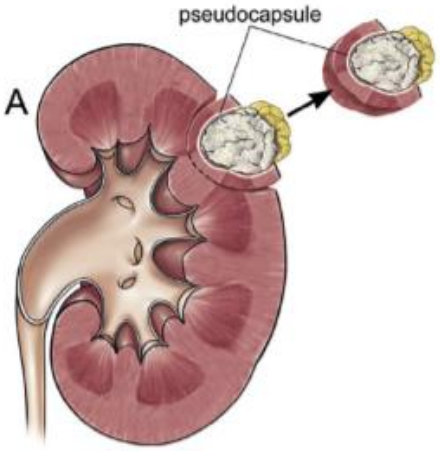
# Highly complex renal tumor

- According to tumor size and location, we can use PADUA or RENAL nephrometry to classify the complexity.
- Highly complex tumor: PADUA score>= 10, or RENAL score>=10
- difficulty in hilar reconstruction and increased risk of complications

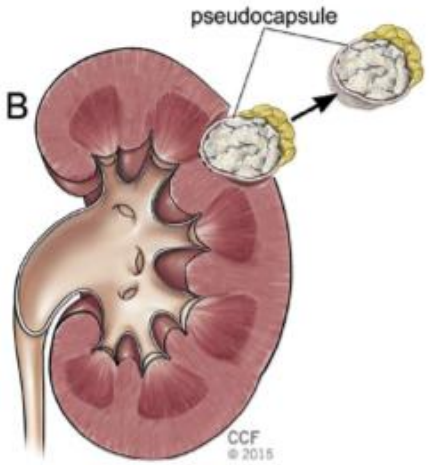



Int J Surg. 2016 Dec;36(Pt C):495-503.

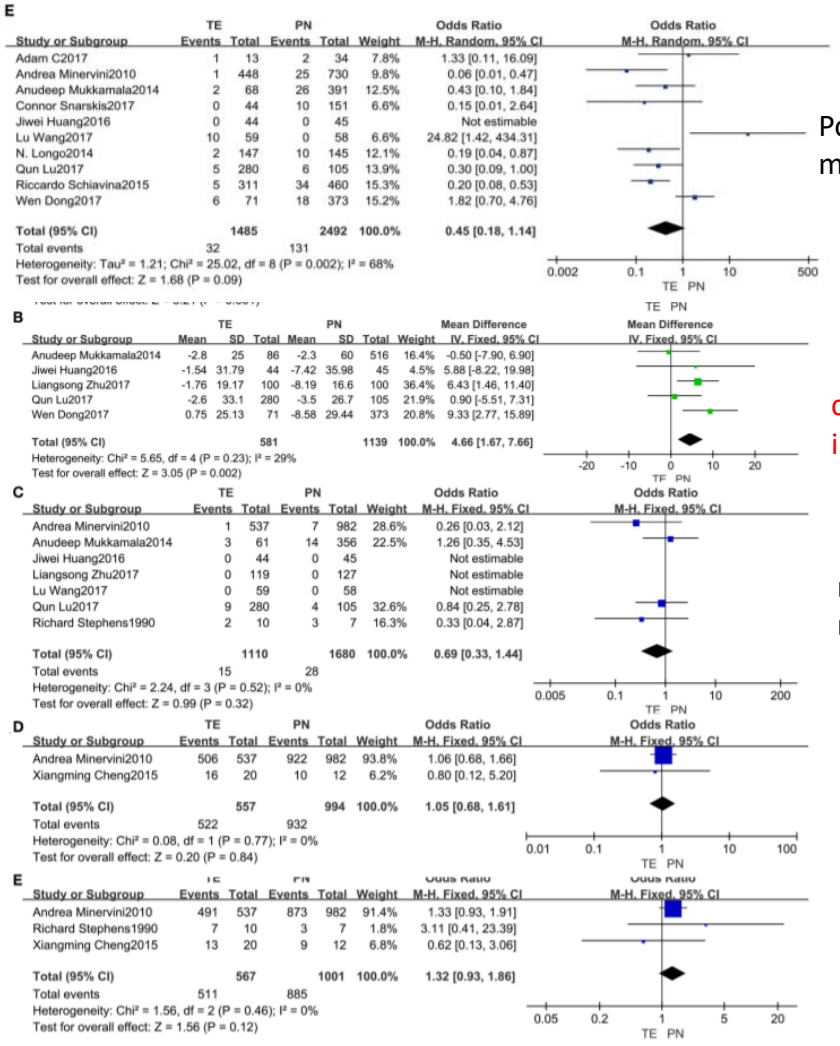
# Tumor Enucleation




Standard
Partial Nephrectomy




Tumor Enucleation




Positive margins

change in eGFR

recurrence rate

5-year CSS

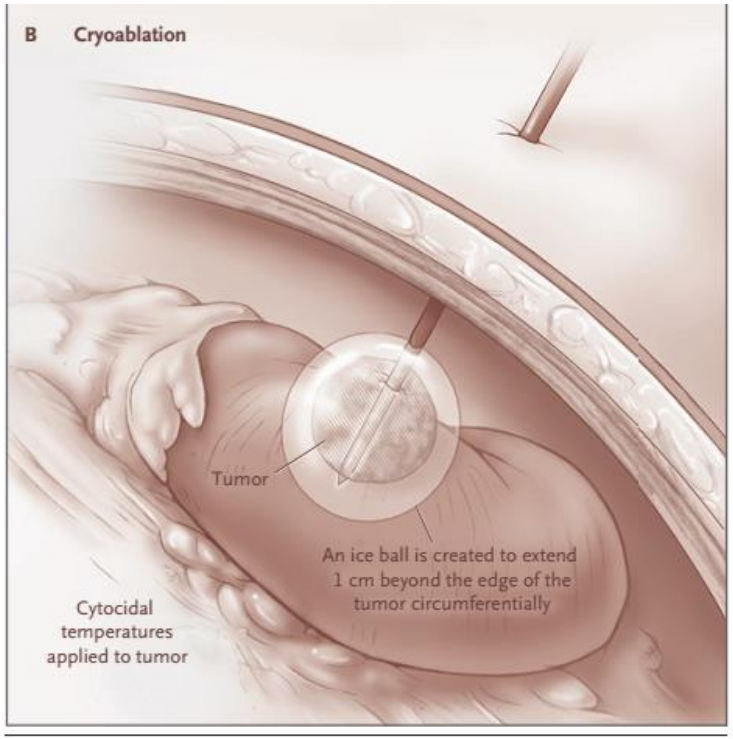
5-year PFS

Urology. 2017 Jan;99:162-168
Front Oncol. 2019; 9: 473.

# Thermal ablation

- Cryoablation (−20 to −40°C) or radiofrequency ablation(RFA) (60 to 100°C)
- Complication: 10%
- Lack of long-term oncological data

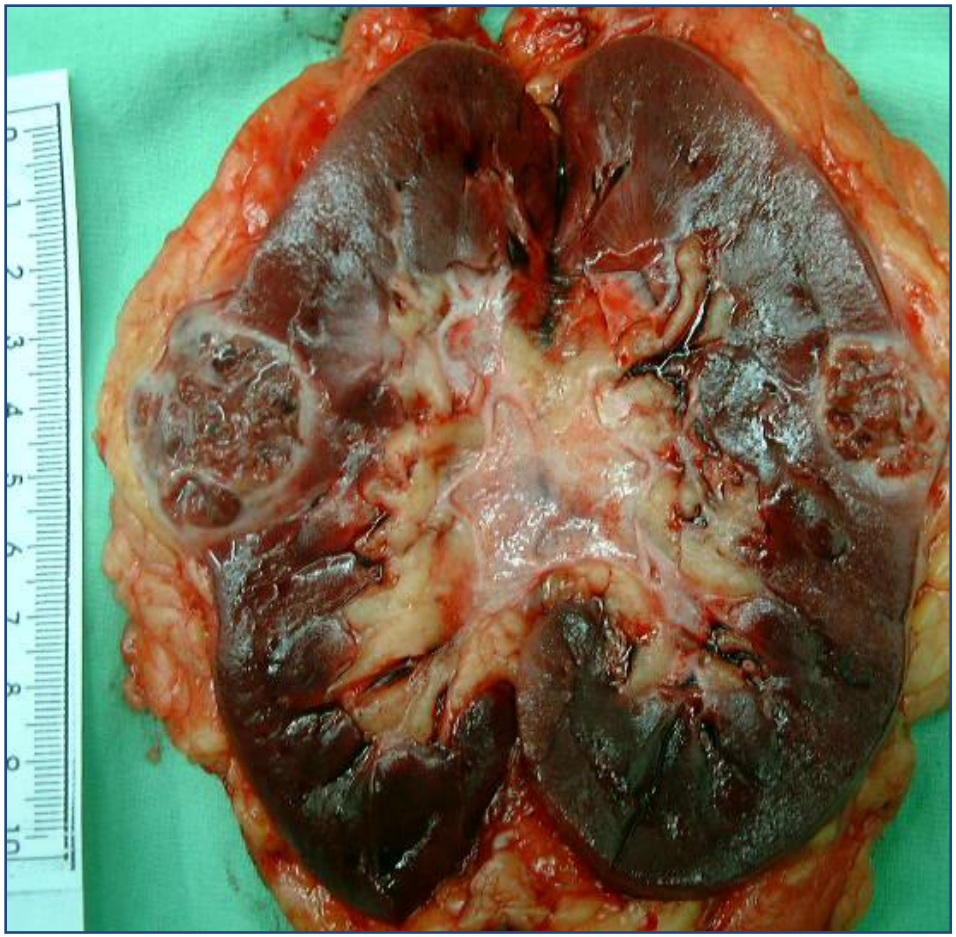
- Indications: elderly, poor candidates for operation, <3cm, alternative option for PN

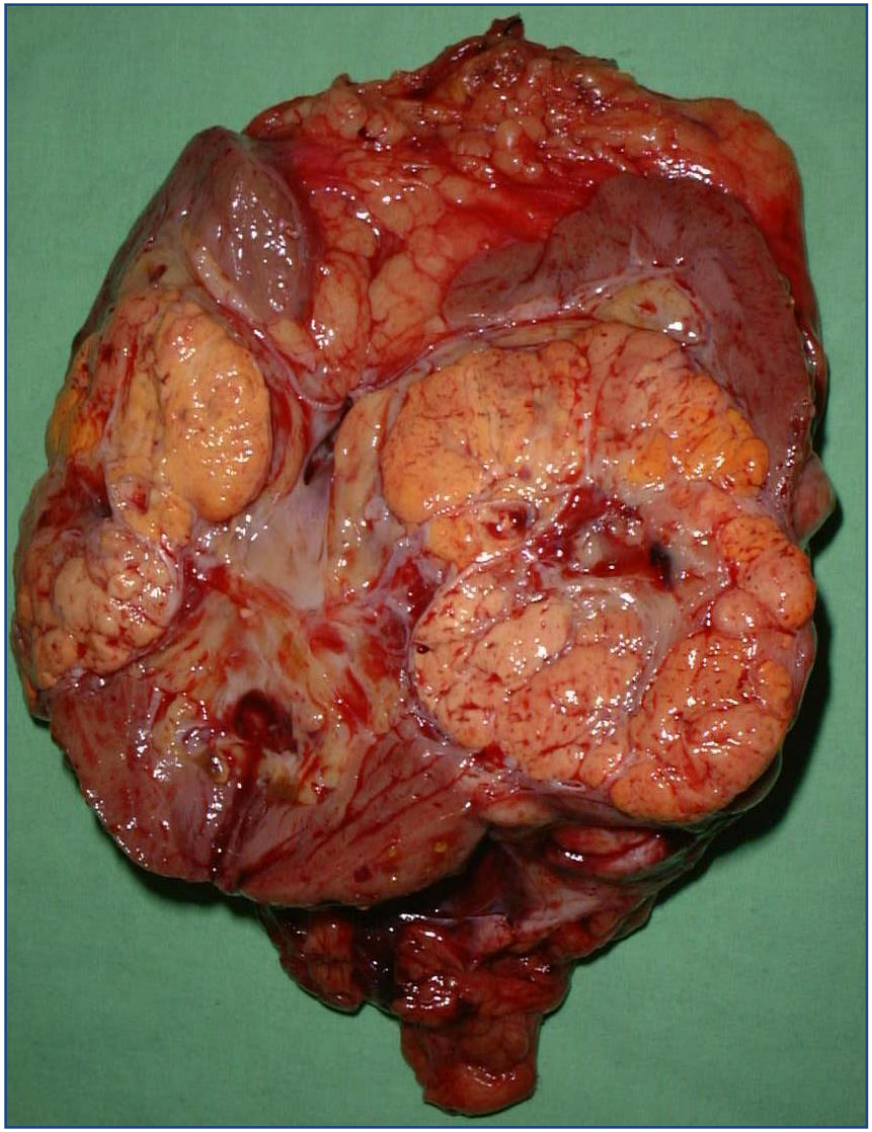


# Radical nephrectomy

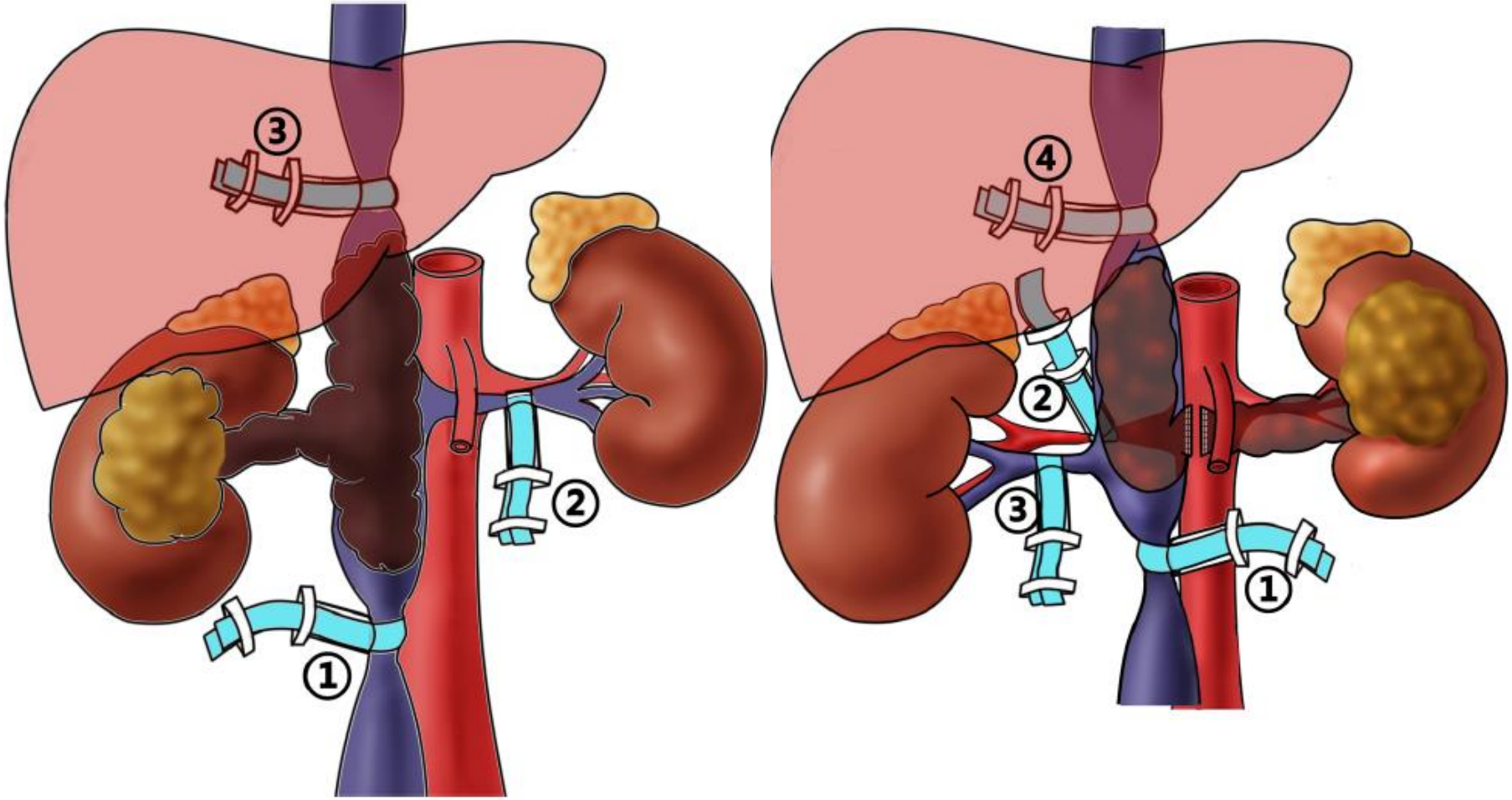
- Indications: only for patients who possess a tumor of significant complexity that is not amenable to PN
- Centrally located small renal mass enmeshed between the branches of the main renal vessels (if excision of the tumor would compromise the major vessels and the collecting-system continuity of the renal remnant)

# Radical nephrectomy





# Technique[8]




[8] Wang B, et al. Robot-assisted Laparoscopic Inferior Vena Cava Thrombectomy: Different Sides Require Different Techniques. *Eur Urol 2016*

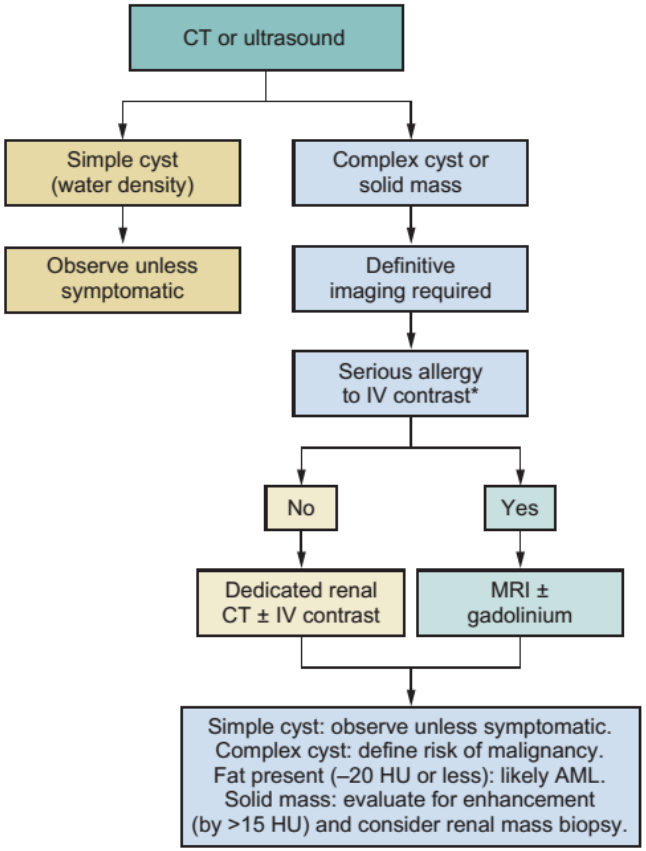



**Figure 57-1. Algorithm for radiographic evaluation of renal masses** **AML, angiomyolipoma; CT, computed tomography; HU, Hounsfiel units; IV, intravenous; MRI, magnetic resonance imaging. *In th presence of chronic kidney disease, the risks of contrast nephropa thy must also be weighed against those of nephrogenic systemi fibrosis associated with gadolinium administration.**

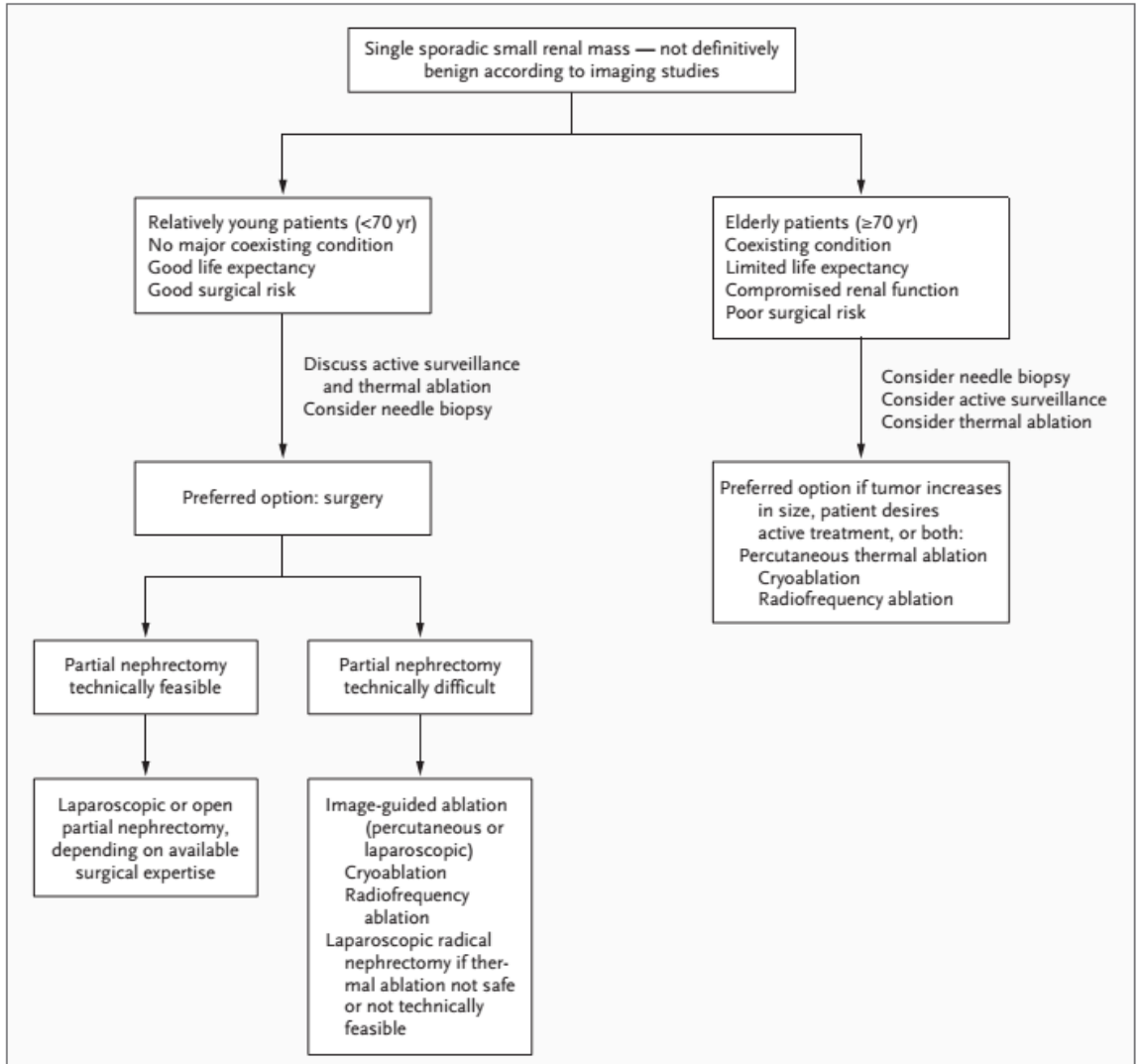
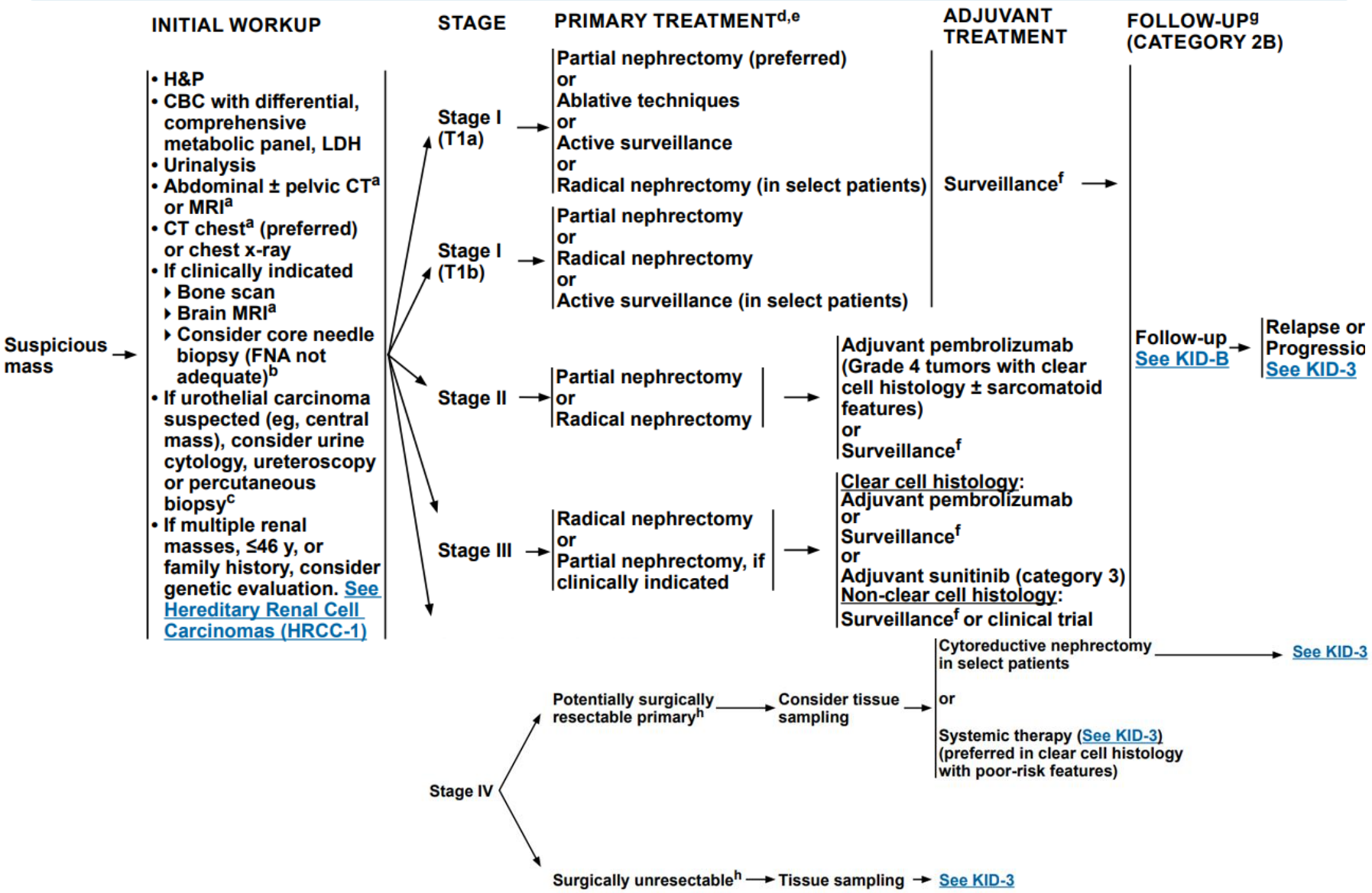
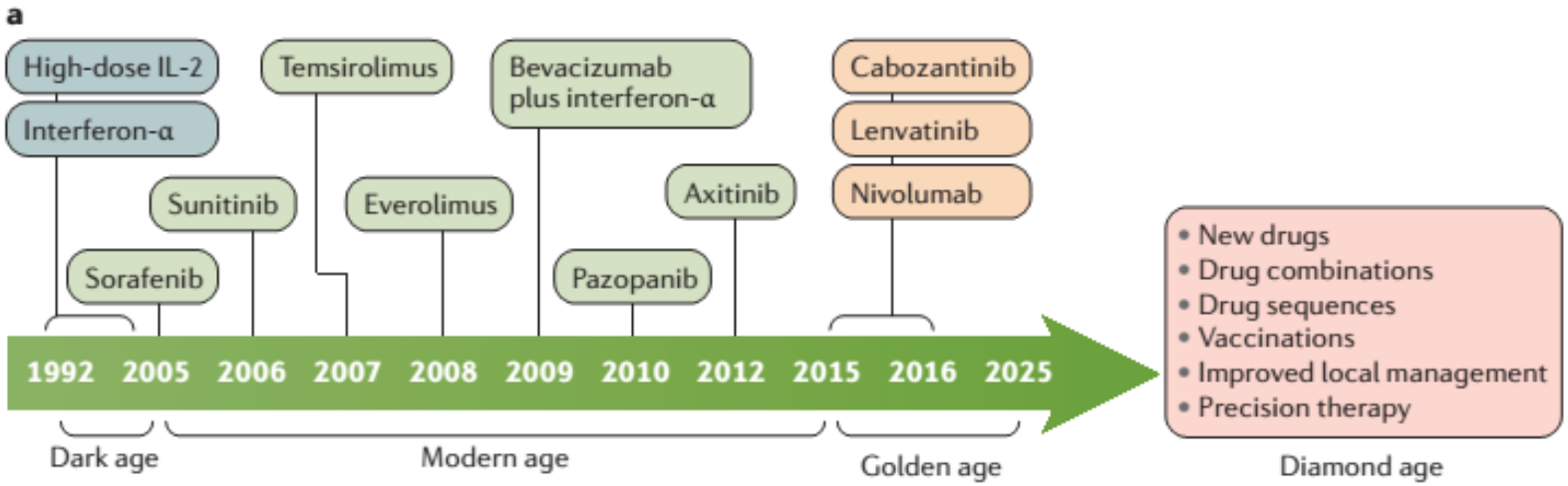



**Figure 4. Suggested Algorithm for Management of a Small Renal Mass.**

If the patient is relatively young (<70 years) and healthy, needle biopsy should be considered and the current literature about active surveillance and thermal ablation should be discussed with the patient, even though active surveillance is not recommended. Tumor size is an important factor that must be considered when finalizing the treatment plan. For example, a spherical 1-cm tumor has a volume of 0.5 ml, whereas a 4-cm tumor has a volume of 33.5 ml, implying considerably greater tumor burden.


INITIAL WORKUP
STAGE
PRIMARY TREATMENT[d,e]
ADJUVANT TREATMENT
FOLLOW-UP[g] (CATEGORY 2B)
Suspicious mass
• H&P
• CBC with differential, comprehensive metabolic panel, LDH
• Urinalysis
• Abdominal ± pelvic CT[a] or MRI[a]
• CT chest[a] (preferred) or chest x-ray
• If clinically indicated
▸ Bone scan
▸ Brain MRI[a]
▸ Consider core needle biopsy (FNA not adequate)[b]
• If urothelial carcinoma suspected (eg, central mass), consider urine cytology, ureteroscopy or percutaneous biopsy[c]
• If multiple renal masses, ≤46 y, or family history, consider genetic evaluation. See Hereditary Renal Cell Carcinomas (HRCC-1)
Stage I (T1a)
Partial nephrectomy (preferred)
or
Ablative techniques
or
Active surveillance
or
Radical nephrectomy (in select patients)
Stage I (T1b)
Partial nephrectomy
or
Radical nephrectomy
or
Active surveillance (in select patients)
Surveillance[f]
Stage II
Partial nephrectomy
or
Radical nephrectomy
Adjuvant pembrolizumab (Grade 4 tumors with clear cell histology ± sarcomatoid features)
or
Surveillance[f]
Stage III
Radical nephrectomy
or
Partial nephrectomy, if clinically indicated
Clear cell histology:
Adjuvant pembrolizumab
or
Surveillance[f]
or
Adjuvant sunitinib (category 3)
Non-clear cell histology:
Surveillance[f] or clinical trial
Follow-up
See KID-B
Relapse or Progressio
See KID-3
Stage IV
Potentially surgically resectable primary[h]
Consider tissue sampling
Cytoreductive nephrectomy in select patients
See KID-3
or
Systemic therapy (See KID-3) (preferred in clear cell histology with poor-risk features)
Surgically unresectable[h]
Tissue sampling
See KID-3

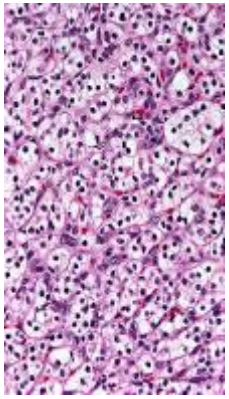
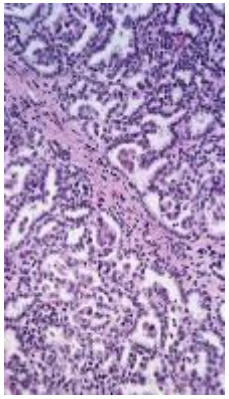
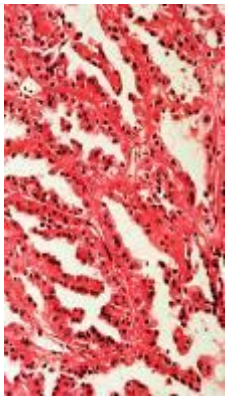
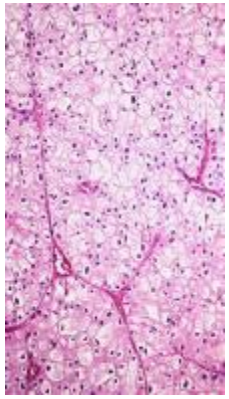
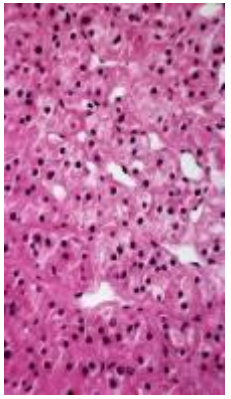
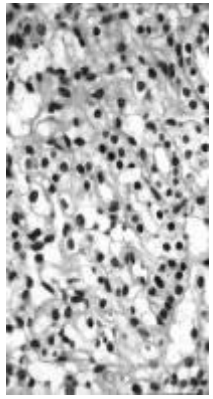
# Therapeutic evolution




*Nature Reviews Disease Primers* 3, 17009,2017

# Histology and Molecular Pathogenesis of RCC

Non-Clear Cell

| Tumor type | Clear Cell | Papillary (type I + II) | | Chromophobic | Oncocytic | Collecting duct[3] |
|---|---|---|---|---|---|---|
| Histology[1] |  |  |  |  |  |  |
| Incidence (%)[2] | 80-90 | 10-15 | | 4–5 | 2–4 | 1 |
| Genetic mutation[1] | *VHL* | *c-MET* | *FH* | *BHD* | *BHD* | |

*BHD* = Birt–Hogg–Dubé; *FH* = fumarate hydratase; *VHL* = von Hippel–Lindau

1. Reproduced from J Urol , 170, Linehan WM, et al. 2163–72, copyright (2003), with permission from the American Urological Association.
2. Motzer RJ, et al. N Engl J Med 1996;335:865–75. 3. Charney DA, Tomasula JR. The Internet Journal of Pathology 2001;2(1). Reproduced with permission

# Biological pathways in renal cell carcinoma

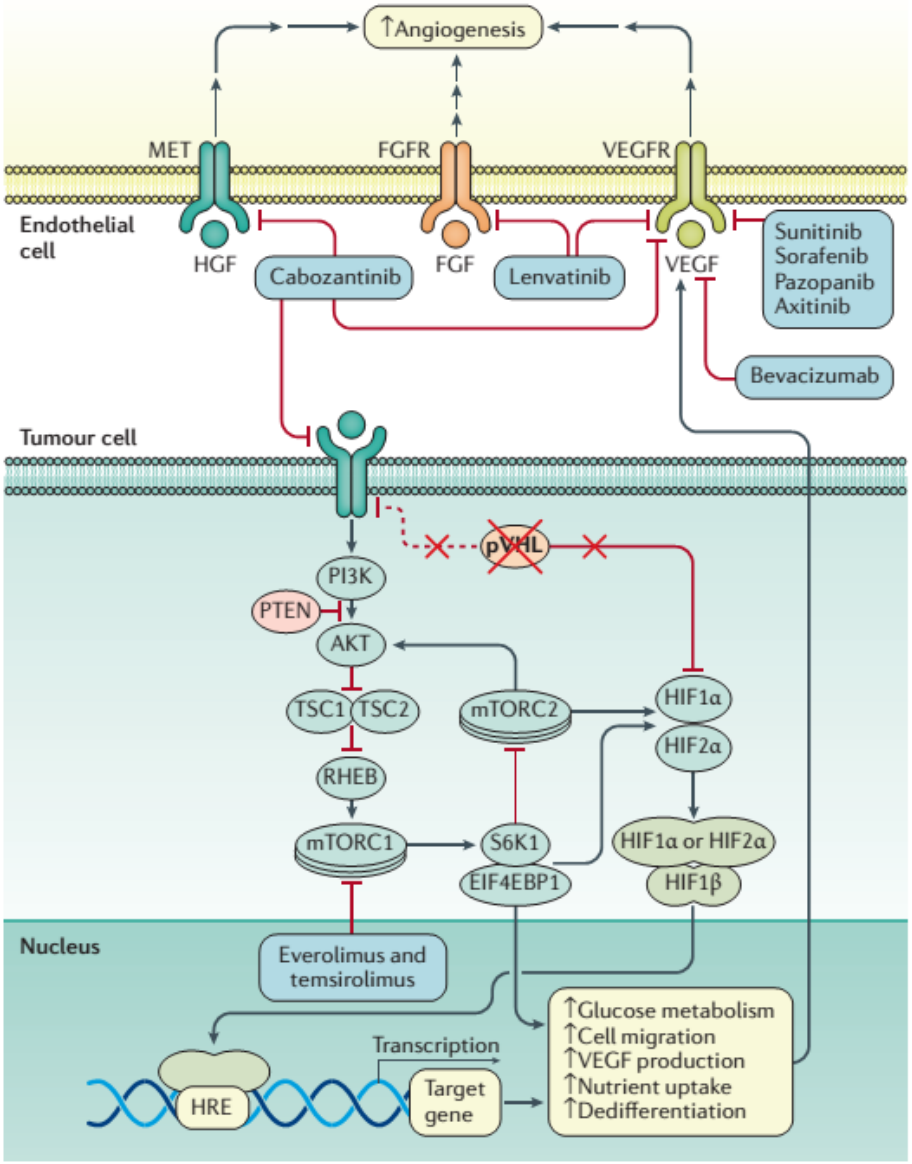



Figure 3 | ***VHL* inactivation in clear cell renal cell carcinoma and its implication in targeted therapy.** Loss of *VHL* (which encodes pVHL) is the most frequent genetic

*Nature Reviews Disease Primers* 3, 17009,2017

# VEGF and mTOR Inhibitors

**VEGF inhibitors**

- Bevacizumab – Neutralizing antibody against VEGF
- Sunitinib
- Sorafenib
- Pazopanib

} Small molecules inhibitors against the VEGF receptor, PDGF receptor, KIT

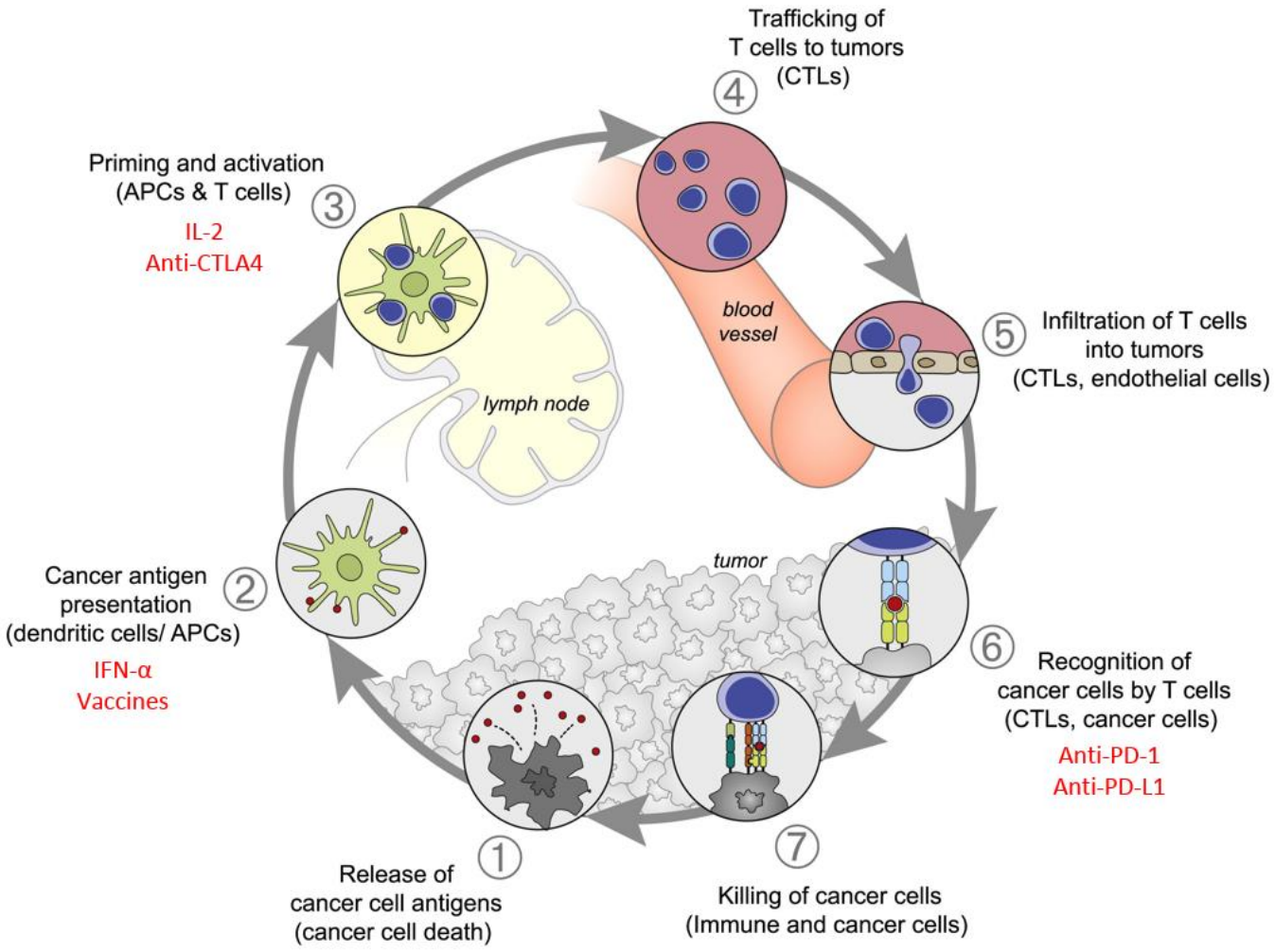
- Axitinib- selective VEGFR
- *Cabozantinib*- VEGFR, MET, AXL inhibitor
- *Lenvatinib*- VEGFR, FGFR, PDGFR, RET, KIT

**mTOR kinase inhibitors**

- Temsirolimus
- Everolimus

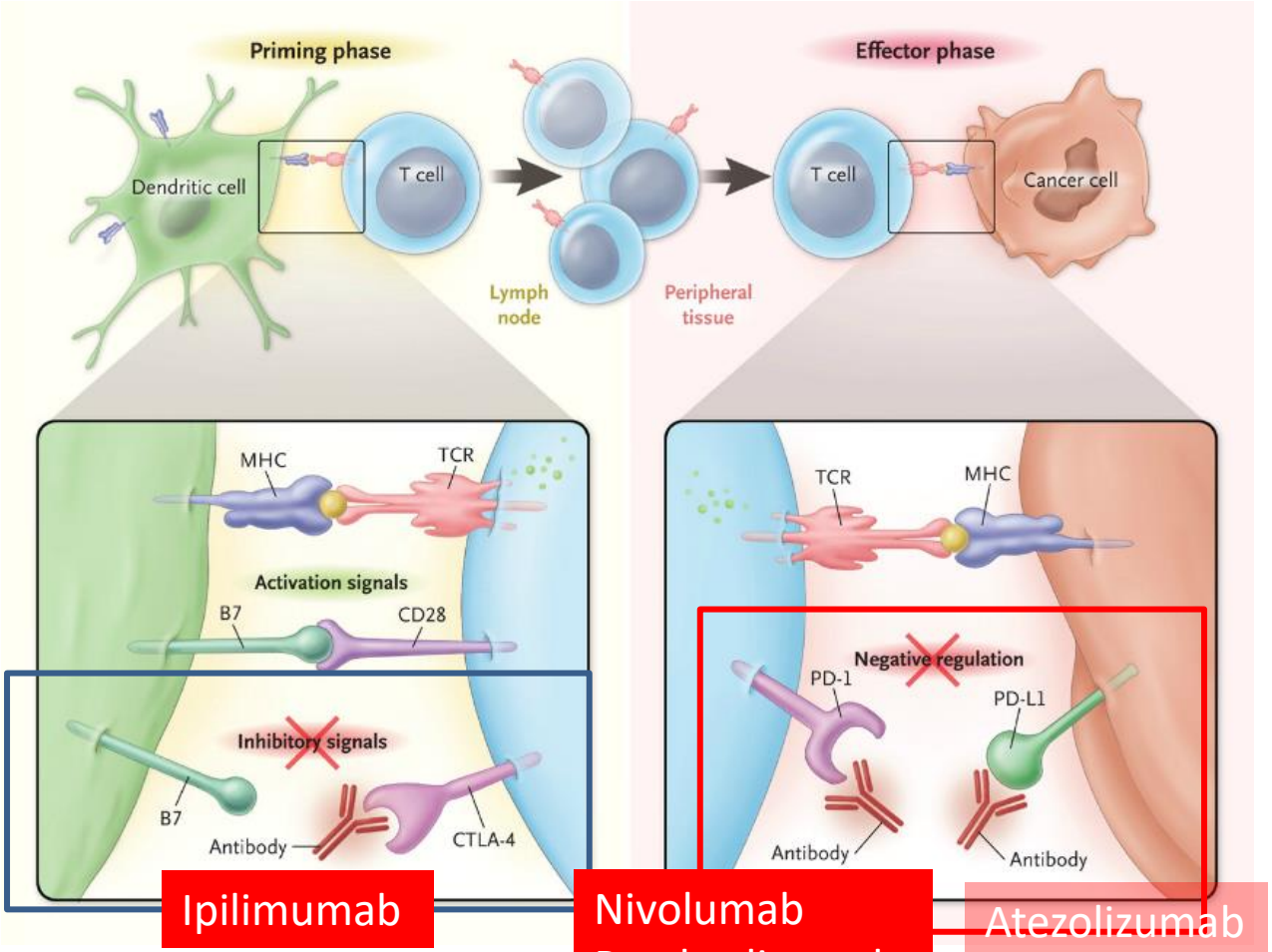
*KDR = kinase domain receptor; mTOR = mammalian target of rapamycin*

# Immunotherapy




Modified from Chen & Mellman (2013) Immunity 39, 1-10.

# CTLA-4 and PD-1 in Tumor Immunotherapy




Ribas A. N Engl J Med. 2012;366:2517-9

# Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic model

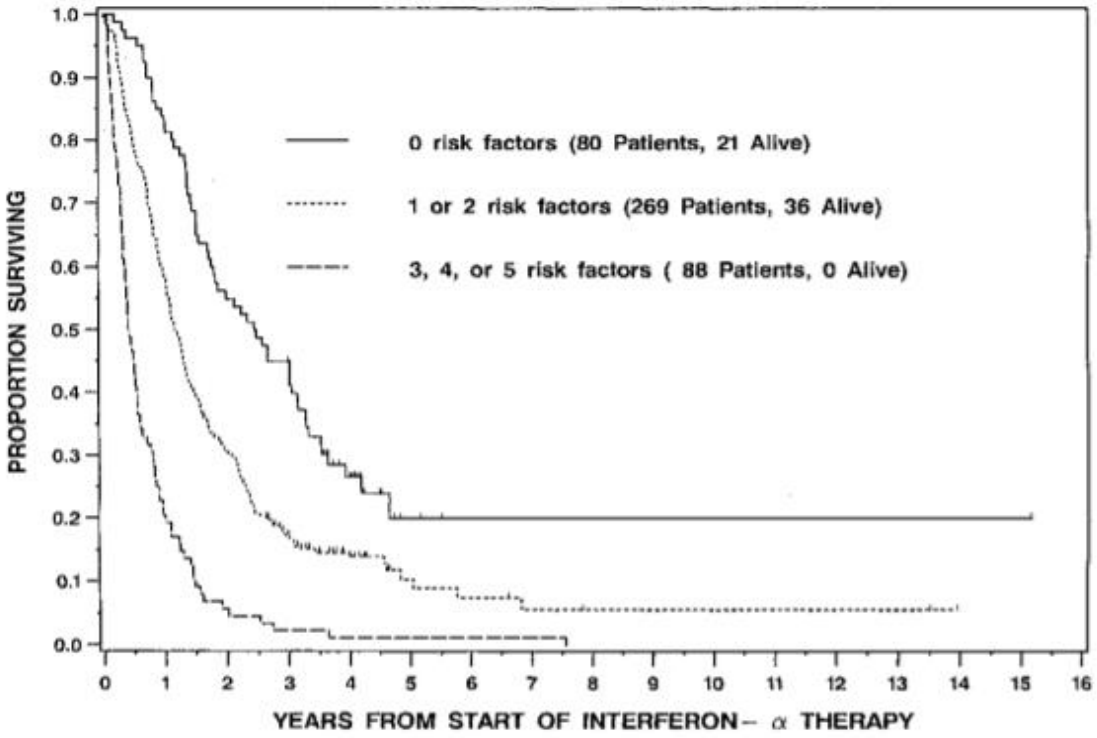
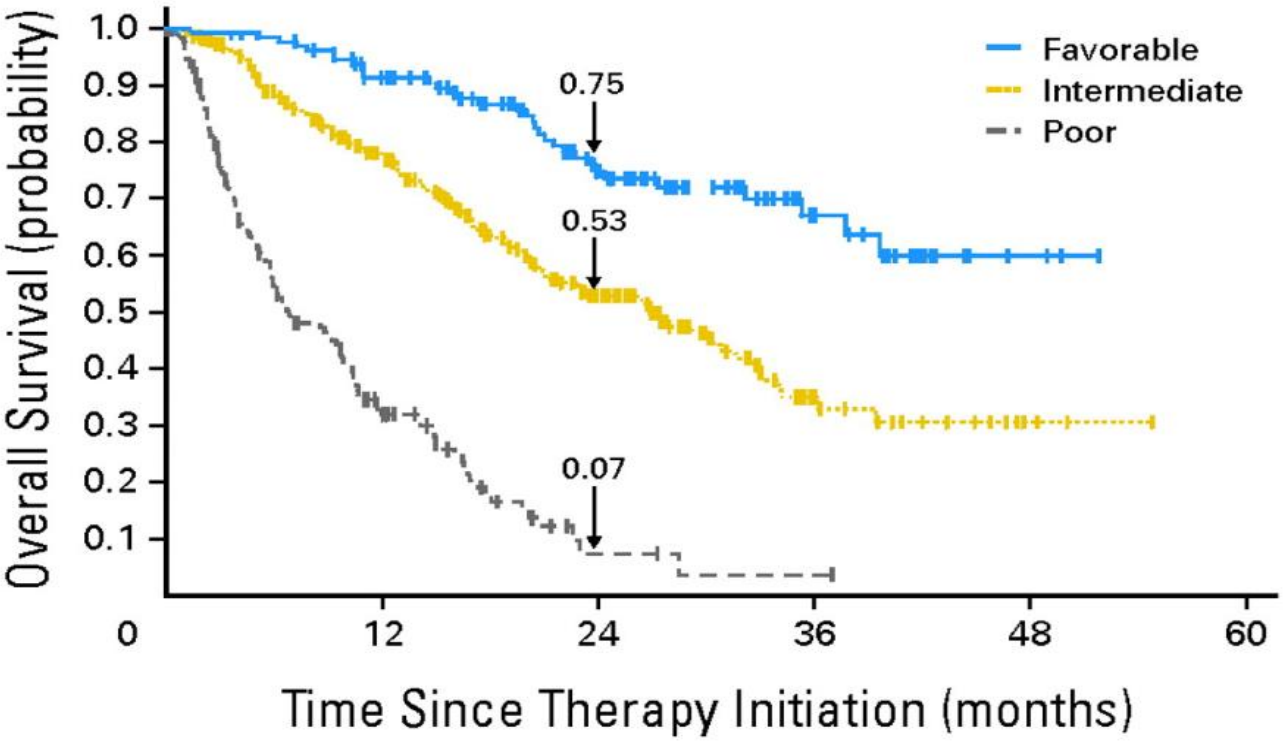



Fig 3. Survival stratified according to risk group (N = 437); 26 patients who were missing one or more of the five risk factors were excluded. | indicates last follow-up.

Motzer, R.J., et al. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol, 2002. 20: 289.

# International Metastatic Renal Cancer Database Consortium(IMDC) model




| No. of events/No. at risk | | | | | |
|---|---|---|---|---|---|
| Favorable | 11/133 | 16/110 | 4/62 | 2/22 | 0/3 |
| Intermediate | 61/301 | 50/182 | 17/82 | 2/18 | 0/3 |
| Poor | 94/152 | 19/36 | 1/3 | 0/1 | 0/0 |

Heng, D.Y., et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol, 2009. 27: 5794.

# MSKCC and IMDC

| Risk models | MSKCC | IMDC ( Heng ) |
|---|---|---|
| Reference | Motzer et al. 2002 | Heng et al. 2009 |
| Systemic treatment | IFN | Sunitinib, sorafenib… |
| Case number | 463 | 645 |
| Factors | Karnorfsky PS < 80%<br>interval < 1yr<br>Ca2+ > 10 mg/dl<br>Hb < LNL<br>LDH >1.5x<br>(>2 cites of organ metastasis) | Karnorfsky PS < 80%<br>interval < 1yr<br>Ca2+ > 10 mg/dl<br>Hb < LNL<br>Neutrophil > UNL<br>Platlet > UNL |
| Risk definition | Favorable 0 risk<br>Intermediate 1-2 risks<br>Poor >=3 risks | Favorable 0 risk<br>Intermediate 1-2 risks<br>Poor >=3 risks |
| Median OS | Favorable 29.6 M<br>Intermediate 13.8 M<br>Poor 4.9 M | Favorable N.R.<br>Intermediate 27M<br>Poor 8.8M |
| Clinical trials | ARCC | CABOSUN, CheckMate214 |

## PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

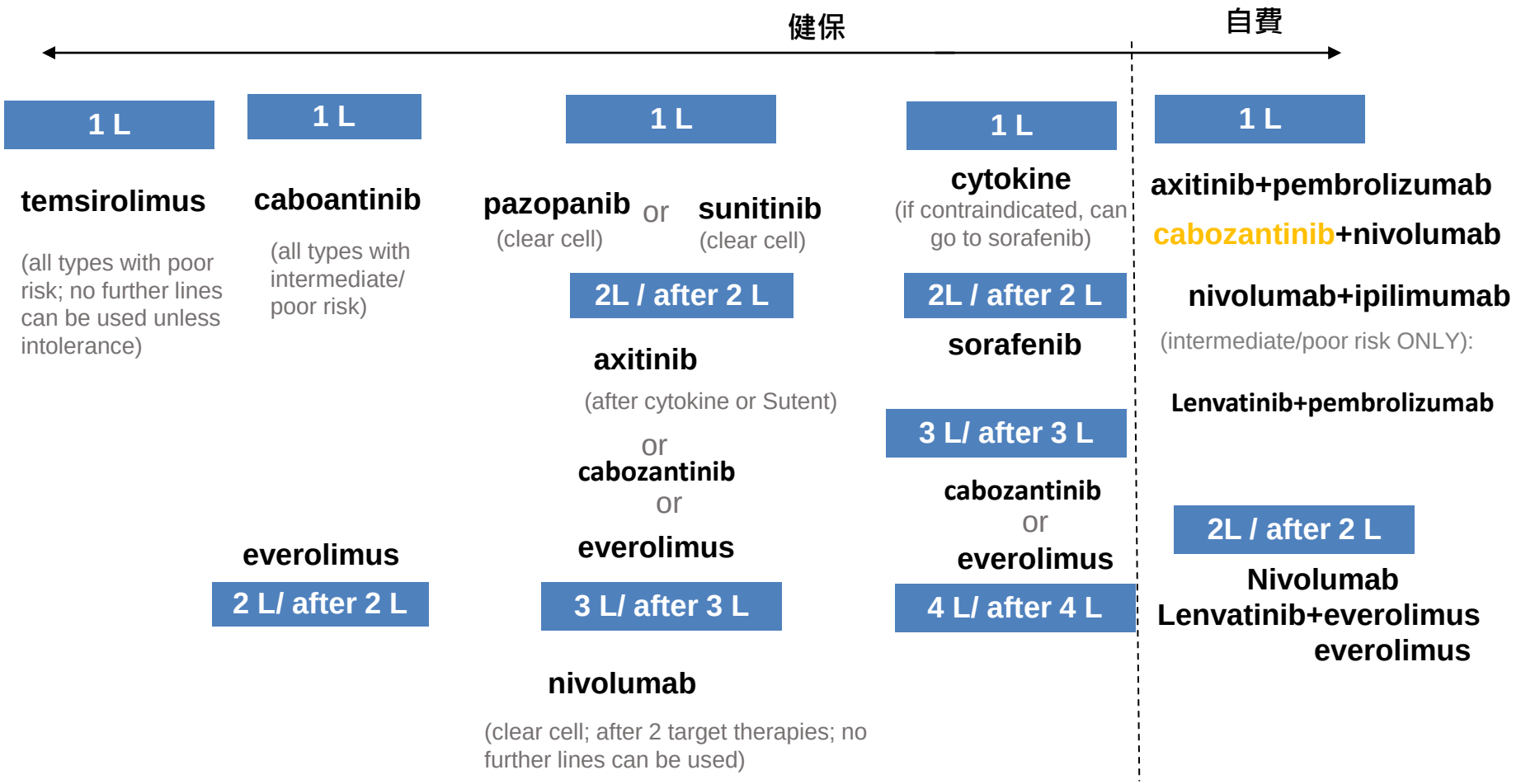
### FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY

| Risk | Preferred Regimens | Other Recommended Regimens | Useful in Certain Circumstances |
|---|---|---|---|
| Favorable[a] | • Axitinib + pembrolizumab[b] (category 1)<br>• Cabozantinib + nivolumab[b] (category 1)<br>• Lenvatinib + pembrolizumab[b] (category 1) | • Axitinib + avelumab[b]<br>• Cabozantinib (category 2B)<br>• Ipilimumab + nivolumab[b]<br>• Pazopanib<br>• Sunitinib | • Active surveillance[c]<br>• Axitinib (category 2B)<br>• High-dose IL-2[d] (category 2B) |
| Poor/ intermediate[a] | • Axitinib + pembrolizumab[b] (category 1)<br>• Cabozantinib + nivolumab[b] (category 1)<br>• Ipilimumab + nivolumab[b] (category 1)<br>• Lenvatinib + pembrolizumab[b] (category 1)<br>• Cabozantinib | • Axitinib + avelumab[b]<br>• Pazopanib<br>• Sunitinib | • Axitinib (category 2B)<br>• High-dose IL-2[d] (category 3)<br>• Temsirolimus[e] (category 3) |

### SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY

| Preferred Regimens | Other Recommended Regimens | Useful in Certain Circumstances |
|---|---|---|
| • Cabozantinib (category 1)<br>• Lenvatinib + everolimus<br>• Nivolumab[b] (category 1) | • Axitinib (category 1)<br>• Axitinib + pembrolizumab[b]<br>• Cabozantinib + nivolumab[b]<br>• Ipilimumab + nivolumab[b]<br>• Lenvatinib + pembrolizumab[b]<br>• Pazopanib<br>• Sunitinib<br>• Tivozanib[g] (category 1)<br>• Axitinib + avelumab[b] (category 3) | • Everolimus<br>• Bevacizumab[f] (category 2B)<br>• High-dose IL-2 for selected patients[d] (category 2B)<br>• Sorafenib (category 3)<br>• Temsirolimus[e] (category 2B)<br>• Belzutifan (category 2B) |

# 台灣晚期或轉移腎細胞癌藥品適應症與健保給付現況



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