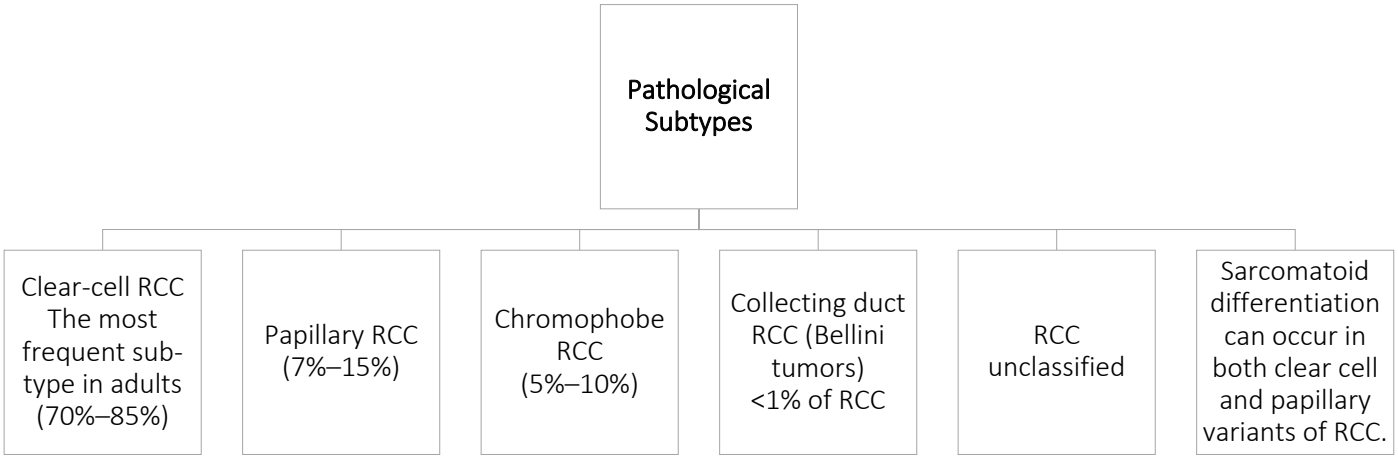
RENAL CELL CARCINOMA

Initial Workup

- **Clinical assessment** including performance status.
- **Imaging:**
  - Abdominal/pelvic CT scan or
  - Abdominal MRI with or without contrast depending on renal insufficiency
  - Chest CT scan
  - PET-CT (is not a standard investigation in the diagnosis and staging of RCC)
  - Bone scan, if clinically indicated.
- **Laboratory Investigations:**
  - CBC
  - Chemistry profile including corrected serum calcium, serum lactate dehydrogenase (LDH)
  - Urine analysis
- **Consider core biopsy to confirm malignancy, indication:**
  - Before treating small lesions with ablative therapies (cryosurgery or radiofrequency) or to guide surveillance
  - In patients with the metastatic disease before commencing systemic treatment.
  - The final histopathological diagnosis, classification, grading and evaluation of prognostic factors are based on the nephrectomy specimen when available.
- **Pathology review.**



Staging

The UICC TNM 2009 staging system should be used.

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤7 cm in greatest dimension, limited to the kidney
T1a	Tumor ≤4.0 cm
T1b	Tumor >4.0 cm but ≤7.0 cm
T2	Tumor >7.0 cm in greatest dimension, limited to the kidney
T2a	Tumor >7 cm but ≤10 cm
T2b	Tumor >10 cm, limited to the kidney
T3	Tumor extends to major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
T3a	Tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat (peri-pelvic) but not beyond Gerota's fascia
T3b	Tumor grossly extends into the vena cava below the diaphragm
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)

Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)

Distant Metastasis (M)	
cM0	Clinically no distant metastasis
cM1	Clinically distant metastasis
pM1	Pathologically proven distant metastasis, e.g. needle biopsy

Cancer Stage Grouping			
Stage I	**T1**	**N0**	**M0**
Stage II	**T2**	**N0**	**M0**
Stage III	**T3**	**N0**	**M0**
	T1-3	**N1**	**M0**
Stage IV	**T4**	**Any N**	**M0**
	Any T	**Any N**	**M1**

Risk Assessment

- Risk assessment models have been developed:
  - To provide prognostic information for patients and
  - To inform the eligibility and risk stratification designs of clinical trials.

Localized Disease

- Two systems can be used to assess the risk of progression in localized tumors:
  - The stage size grade and necrosis (SSIGN) score and
  - The UCLA Integrated Staging System (UISS)

SSIGN score for localized RCC

Feature		Score
Pathological T category of the primary tumor (TNM 2002).	PT1a	0
	pT1b	2
	pT2	3
	pT3a-b	4
Regional lymph node status (TNM 2002)	pNx or pN0	0
	pN1 or pN2	2
Tumor size	< 10 cm	0
	≥ 10 cm	1
Nuclear Grade	1 or 2	0
	3	1
	4	3
Histological tumor necrosis	No	0
	Yes	1

Scores	Group	3-year Metastasis-Free Survival (%)
0-2	Low risk	97.1
3-5	Intermediate risk	73.8
≥ 6	High risk	31.2

Reference: Annals of Oncology 23 (Supplement 7): vii65–vii71, 2012

Advanced Disease

- Prognostic models were first built when immunotherapy was the standard therapy.
- The Memorial Sloan-Kettering Cancer Center (MSKCC) or Motzer score was the standard system.
- The MSKCC score has now been validated and updated to stratify risk profiling of RCC.

- Patients are stratified according to the presence of six risk factors:
  - Karnovsky performance status (PS) <80%.
  - Hemoglobin is less than the lower limit of normal.
  - Time from diagnosis to treatment <1 year (In reference to cytokine therapy)
  - Corrected calcium above the upper limit of normal.
  - Platelets are greater than the upper limit of normal.
  - Neutrophils are greater than the upper limit of normal.

The number of risk factors present is added up and the risk is stratified as follows:

Risk group	Number of risk factors	Two-year overall survival (%)
Favorable	0	75
Intermediate	1 – 2	53
Poor	3 – 6	7

Management of Local/Loco-Regional Disease

I. T1 tumors (<7cm)

Partial Nephrectomy

Partial nephrectomy is recommended as the preferred treatment option for:

- Tumors confined to the organ and measuring up to 7 cm.
- Patients with compromised renal function, solitary kidney or bilateral tumors.

Radiofrequency or Cryo-ablative Treatments

Radiofrequency or cryo-ablative treatments are alternative approaches, especially in patients with:

- Small cortical tumors,
- Hereditary RCC and
- Multiple bilateral tumors.

Active Surveillance

Active surveillance may be opted for:

- Elderly patients, and
- Patients with substantial co-morbidities who are expected to have a short life span.

II. T2 Tumors (>7 cm)

Laparoscopic radical nephrectomy is the preferred option.

III. Locally advanced RCC (T3 and T4)

Open Radical Nephrectomy

Open radical nephrectomy remains the standard of care even though the laparoscopic approach can be considered.

Systematic adrenalectomy or extensive lymph node dissection are not recommended when abdominal CT shows no evidence of adrenal or lymph node invasion.

Adjuvant Treatment

There is no recommended adjuvant treatment, although many adjuvant trials are ongoing.

Neo-adjuvant Treatment

Neo-adjuvant approaches are still experimental, especially for resectable tumors.

It should not be proposed outside the context of clinical trials.

Management of Metastatic Disease

Role of Surgery

Cytoreductive Nephrectomy

- Cytoreductive nephrectomy is recommended in patients with:
  - Good PS and
  - Large primary tumors, and
  - Patients with a symptomatic primary lesion.
- Cytoreductive nephrectomy is not recommended in patients with poor PS.

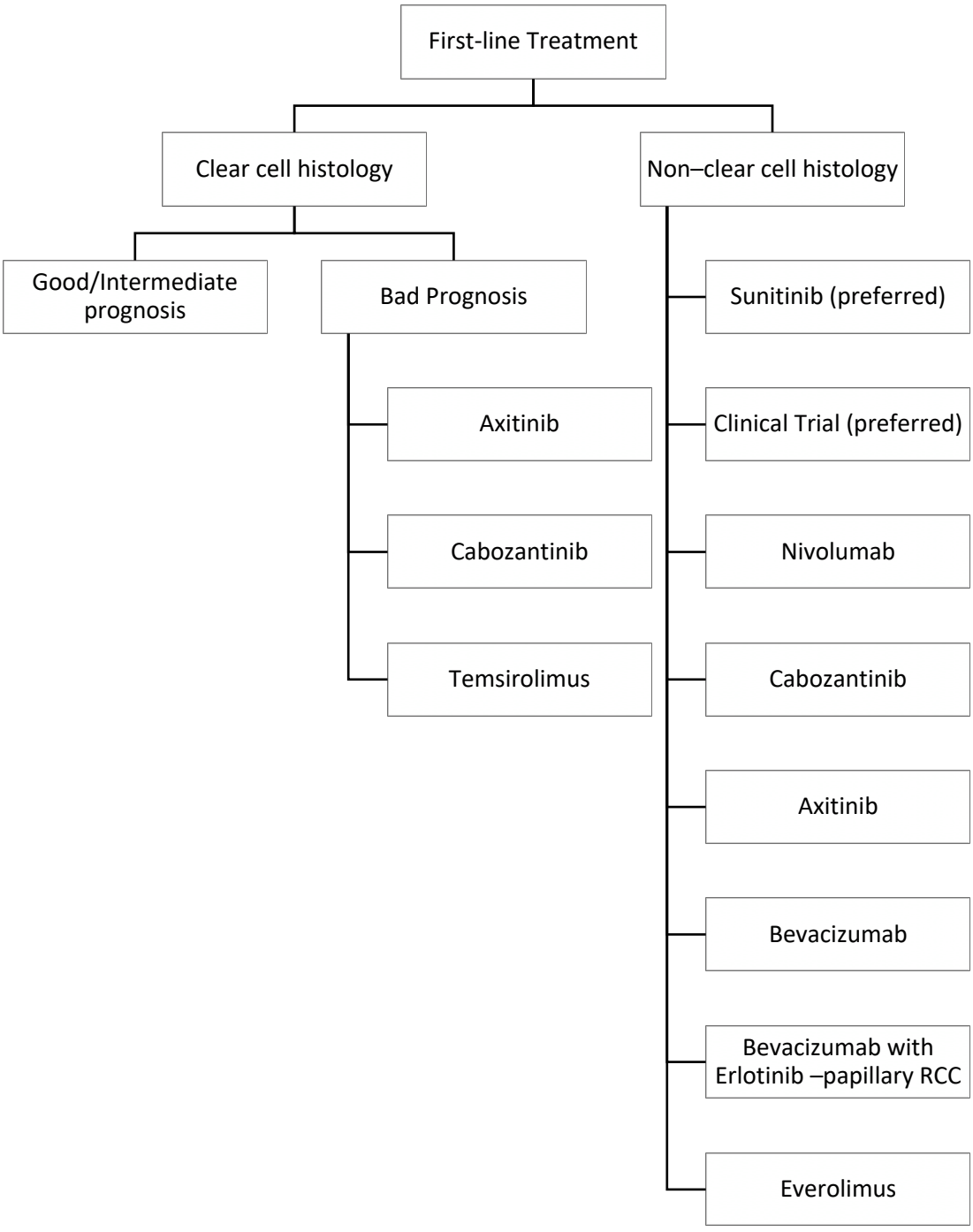
Metastasectomy

- Metastasectomy can be considered for select patients with:
  - Solitary or an easily accessible pulmonary metastasis,
  - Solitary resectable intra-abdominal metastases,
  - Long disease-free interval after nephrectomy or
  - Partial response in metastases to immunotherapy or targeted therapy.
- Recent retrospective and non-randomized studies of patients with metastatic RCC(mRCC) have demonstrated prolonged median survival in those with metachronous lung metastases and an interval of at least 2 years.
- Metastasectomy may provide a potential survival benefit for a selected group of patients with lung metastases only, a long disease-free interval and a response to earlier therapies.

Systemic Treatment

- Recommendations mainly relate to clear-cell histology, since most of the pivotal trials have been done in this common histological sub-type. Also, our recommendation will differ according to risk stratification.

1) First-line treatment for patients with good or intermediate Prognosis



1 -Sunitinib (category 1)

2- Bevacizumab – with Interferon Alfa 2-b

3 -pazopanib (category 1)

2) Second-line treatment

Second line treatment

Previous treatment with VEGF- Rs pathway

Previous treatment with cytokines

1-Nivoulumab (preferred) 2-Axitinib 3-Everloimus

1- Sunitinib (preferred) 2- Clinical Trial (preferred) 3- Nivolumab 4 -Cabozantinib 5 -Axitinib 6-Sorafenib

3) Third-line Treatment

- Further to the second line, enrollment into clinical trials is recommended where possible.
- In patients already treated with two tyrosine kinase inhibitors (TKIs) and vascular endothelial growth factor (VEGF) targeted therapy, nivolumab is recommended.

- Supporting data:
  - This recommendation is based on the result of the pivotal trial CHECKMATE 025.
  - Nivolumab had shown OS compared with everolimus and thus the NCCN has included nivolumab as the preferred subsequent therapy option (category 1).

Supportive Treatment

- **Radiotherapy** is an effective tool for palliation of local; symptomatic metastatic diseases that may improve:
  - Bone pain score and
  - Quality of life for brain and spinal cord compression.
- **Bisphosphonate therapy** with zoledronic acid has been shown to reduce skeletal-related

- **Denosumab**, RANKL-RANK inhibitor is available for use in some patients not suitable for bisphosphonates.

Response Evaluation and Follow Up

- The follow-up scheme for localized RCC following surgery should be dependent on the therapeutic possibilities upon recurrence.
- CT scans of thorax and abdomen are routinely performed, with time intervals depending on risk factors.
- Those cases will be under the follow-up under our surgical team.
- Long-term follow-up is proposed in some institutions, due to the possibility of late relapse, but its benefit has never been demonstrated.
- During systemic therapy in mRCC patients, 2-4 monthly follow-up schemes with CT scan should be advised to determine response and resistance.

Sunitinib (Sutent):

- The FDA has approved sunitinib (Sutent) for use as adjuvant therapy in patients with renal cell carcinoma (RCC) who have done nephrectomy and are high risk for recurrence.
- Supporting Evidence:
    - The approval for sunitinib is based on findings from the phase III S-TRAC trial, which were presented at the 2016 ESMO Congress and published in the *New England Journal of Medicine*.
    - In the study, adjuvant sunitinib prolonged disease-free survival (DFS) by 1.2 years compared with placebo following nephrectomy for patients with high-risk clear cell RCC.
    - After a median follow-up duration of 5.4 years, the median DFS was 6.8 years in the sunitinib arm compared with 5.6 years with placebo (HR, 0.76; 95% CI, 0.59-0.98; *P* = .03).
    - In higher-risk patients, the median DFS was 6.2 versus 4.0 years for sunitinib and placebo, respectively (HR, 0.74; 95% CI, 0.55-0.99; *P* = 0.04).
    - Grade 3/4 adverse events (AEs) were experienced by 63.4% of patients in the sunitinib group compared with 21.7% in the placebo arm.
    - Frontline treatment with the combination of nivolumab (Opdivo) and ipilimumab (Yervoy) reduced the risk of death by 32% compared with sunitinib (Sutent) for patients with metastatic renal cell carcinoma (mRCC), according to findings from the CheckMate 214 study presented at the 2017 ESMO Congress.