RENAL CELL CANCER

General Overview

- Peak incidence is between 60-70 years, with a slight predominance of men (3:2)
- Diagnosis is often made upon accidental finding on imaging for other reasons
- Clear-cell RCC is the most common histological subtype (>70%). These tumors all have loss of the Von Hippel Lindau (VHL) gene, which mimics an hypoxic state. Among others, this leads to an upregulation of HIF-2 alpha, VEGF and an immune suppressive micro-environment, which sensitizes these tumors to VEGF and HIF-2 alpha inhibitors, as well as immune therapies.
- Other histological subtypes include papillary, chromophobe and sarcomatoid RCC, as well as several others. Several molecular drivers are emerging (2022 WHO classification)

Staging (AJCC Version 8) and Prognosis

- CT thorax-abdomen for staging. DMSA renal scan pre-operatively in case of impaired renal function. MR abdomen in case of indeterminate renal mass or possible venous involvement.
- Tissue diagnosis is mandatory. This can be done post-operatively on the resection specimen. If no resection is done, percutaneous core biopsy is necessary before starting treatment or active surveillance (not useful for cystic masses without significant solid component)
- In advanced disease: full lab set including International Metastatic Renal Cell carcinoma Database consortium (IMDC) parameters and immune bilan (glucose, TSH, fT4, HIV-HBV-HCV serology)
- IMDC risk factors: anemia, elevated neutrophils, elevated platelets, Karnofsky ≤70, hypercalcemia, interval between diagnosis and systemic treatment < 1 year): Good risk (0 risk factors), Intemediate risk (1-2 risk factors), Poor risk (3-6 risk factors)
- Referral for genetic screening if ≤ 46 years, bilateral or multifocal RCC, first-/second-degree relative with RCC or known familial cancer syndrome.
- Discuss at MTB somatic genetic screening for molecular drivers

Primary Tumor (T)	Regional Lymph Nodes (N)	Distant Metastasis (M)
Tx: Primary tumor cannot be assessed **T0**: No evidence of primary tumor **T1**: Tumor ≤ 7cm limited to the kidney **T1a**: ≤ 4 cm **T1b**: >4cm but ≤ 7 cm **T2**: Tumor > 7 cm limited to the kidney **T2a**: > 7 cm but ≤ 10 cm **T2b**: > 10 cm limited to the kidney **T3**: Extends into major veins or perinephric tissues (not into ipsilateral adrenal gland) **T3a**: Extends into the renal vein or its segmental branches, the pelvicalyceal system or invades perirenal and/or renal sinus fat, but not beyond Gerota fascia	**Nx**: LN cannot be assessed **N0**: no regional LN **N1**: M+ in regional LN	**M0**: no distant M+ **M1**: distant M+

Update: March 2024

T3b: Tumour grossly extends into the vena cava below diaphragm
T3c: Tumour grossly extends into vena cava above the diaphragm or invades the wall of the vena cava
T4: Invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)

- Anatomic Stage
  - Stage I: T1N0M0
  - Stage II: T2N0M0
  - Stage III: T3N0M0, T1-3N1M0
  - Stage IV: T4 Any N M0, Any T Any N M1

Treatment

- Partial nephrectomy when possible. Lymphadenectomy only for clinically enlarged lymph nodes.
- Active surveillance can be discussed in frail or elderly patients with cT1a renal masses.
- Local ablation results in less morbidity but higher recurrence compared with surgery. It can be offered in case of poor performance status, multiple RCC, poor kidney function or other risk factors for surgery (cryoablation up to 4cm, thermal ablation up to 3cm).
- In oligometastatic IMDC good risk patients, upfront cytoreductive nephrectomy and radical treatment of all metastases (resection or stereotactic body radiotherapy) can be discussed. These patients may receive adjuvant pembrolizumab for 1 year (Choueiri *et al*, NEJM 2021)
- In oligometastatic IMDC good risk patients not fit or willing to undergo surgery, observation until progression before starting systemic therapy can be discussed.
- Other patients should receive systemic therapy first (Méjean *et a*l, NEJM 2018). In patients with a deep and stable response after 6-12 months, radical treatment of visible disease can be discussed
- First-line therapy is a combination of either two immune checkpoint inhibitors or a VEGFR-inhibitor with immune checkpoint inhibitor (lenvatinib-pembrolizumab, cabozantinib-nivolumab, axitinib-pembrolizumab).
  - Ipilimumab-nivolumab only for IMDC intermediate and poor risk. It is usually preferred because of the duration of responses and long-term tolerability. (Motzer *et al*, NEJM 2018)
  - A combination with VEGFR-inhibitor is preferred for patients who need a quick response or at high risk for auto-immune toxicity (e.g. lenvatinib-pembrolizumab, saving cabozantinib for second line). (Motzer *et al*, NEJM 2021; Choueiri *et al*, NEJM 2015)
  - If contra-indication for immune checkpoint inhibitor: cabozantinib in IMDC intermediate/poor risk patients and pazopanib in IMDC good risk patients (Choueiri *et al*, J Clin Oncol 2017)
- Second and further line therapies consist of sequencing of VEGFR-inhibitors (cabozantinib, pazopanib, sunitinib, axitinib) as long as there is clinical benefit. Use cabozantinib as second line for fit patients, if not given in first line.
- Everolimus is used after VEGFR-TKIs
- Non-clear-cell RCC:
  - Lenvatinib-pembrolizumab 1st line, cabozantinib 2nd line.
  - If sarcomatoid features (regardless of dominant histological subtype): ipilimumab-nivolumab

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Follow-up Localized RCC

- Active surveillance: tailored approach.
- Low risk of recurrence:
  - ccRCC: Leibovich 0-2
  - non-ccRCC: pT1a-T1b pNx-0M0 and histological grade 1-2
- Intermediate risk of recurrence:
  - ccRCC: Leibovich 3-5
  - non-ccRCC: pT1b pNx-0 and/or histological grade 3-4
- High risk of recurrence:
  - ccRCC: Leibovich ≥6
  - non-ccRCC: pT2-pT4 any histological grade or pTany pN1 cM0 any histological grade

Risk profile (*)	Oncological follow-up after date of surgery								
	3 mo	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo	> 3 yr	> 5 yr
Low risk	-	CT	-	CT	-	CT	-	CT / 2 yrs	-
Intermediate risk	-	CT	CT	-	CT	-	CT	CT / 1 yrs	CT / 2 yrs
High risk	CT	CT	CT	CT	CT	-	CT	CT / 1 yrs	CT / 2 yrs

What's new ?

- ^{89}Zr-DFO girentuximab PET CT for clear-cell RCC imaging (not in the clinic yet)
- Belzutifan, a HIF-2 alpha inhibitor, for pretreated clear-cell RCC or Von Hippel Lindau disease related RCC (not reimbursed in Belgium) (Albiges et al, ESMO LBA88 2023, LITESPARK-005)