RENAL CELL CARCINOMA

Another “most fascinating” cancer entity.

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CONFLICT OF INTEREST DISCLOSURE

Dr Christoph Oing

Personal financial interests

Institutional financial interests
- None

Non-financial interests / Leadership role medical societies non-remunerated
- Chairman “Junge DGHO” of the German Society of Hematology and Oncology (DGHO)
- ESMO YOC member

Other
- Travel and conference attendance: IPSEN (2017)
KIDNEY TUMOURS

Clinical presentation

- Macroscopic hematuria
- Lower back pain
- Palpable lumbar mass
- Anemia
- Fatigue

- Incidentally, asymptomatic (ultrasound, MR)
KIDNEY TUMOURS

Diagnostic work-up

- RCC suspected:
  - Abominopelvic CT (contrast-enhanced) or
  - MRI
  - Chest X-ray
  - Bone scan (if clinically indicated)

- Who needs a biopsy?
  - If surgery anyways → No

- But you need a biopsy...
  - To assess indeterminate (small) renal masses
  - To select most suitable therapy strategy (“Treat or not to treat”)
Many different histologies

90% of kidney cancers RCC

Different clinical behaviour

- Clear cell carcinoma
- Papillary type I
- Papillary type II
- Chromophobe
- Collective ducts
- Others

The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs—Part A:...
KIDNEY CANCER

Epidemiology

- ~13,000 new cases each year in the UK\(^1\)
- 4,619 kidney cancer deaths in 2016 in the UK\(^1\)
- ~400,000 new cases each year worldwide\(^2\)
- ~175,000 kidney cancer deaths worldwide\(^2\)
- Approximately 3% of all adult cancers
- \(♂ : ♀ = 1.5 : 1\)

<table>
<thead>
<tr>
<th>CANCER SITE</th>
<th>NO. OF NEW CASES (% OF ALL SITES)</th>
<th>NO. OF DEATHS (% OF ALL SITES)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>2,093,876 (11.6)</td>
<td>1,761,007 (18.4)</td>
</tr>
<tr>
<td>Breast</td>
<td>2,088,849 (11.6)</td>
<td>626,679 (6.6)</td>
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<tr>
<td>Prostate</td>
<td>1,276,106 (7.1)</td>
<td>358,989 (3.8)</td>
</tr>
<tr>
<td>Colon</td>
<td>1,096,601 (6.1)</td>
<td>551,269 (5.8)</td>
</tr>
<tr>
<td>Nonmelanoma of skin</td>
<td>1,042,056 (5.8)</td>
<td>65,155 (0.7)</td>
</tr>
<tr>
<td>Stomach</td>
<td>1,033,701 (5.7)</td>
<td>782,685 (8.2)</td>
</tr>
<tr>
<td>Liver</td>
<td>841,080 (4.7)</td>
<td>781,631 (8.2)</td>
</tr>
<tr>
<td>Rectum</td>
<td>704,376 (3.9)</td>
<td>310,394 (3.2)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>572,034 (3.2)</td>
<td>508,585 (5.3)</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>569,847 (3.2)</td>
<td>311,365 (3.3)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>567,233 (3.1)</td>
<td>41,071 (0.4)</td>
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<tr>
<td>Bladder</td>
<td>549,393 (3.0)</td>
<td>199,922 (2.1)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>509,590 (2.8)</td>
<td>248,724 (2.6)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>458,918 (2.5)</td>
<td>432,242 (4.5)</td>
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<tr>
<td>Leukemia</td>
<td>437,033 (2.4)</td>
<td>309,006 (3.2)</td>
</tr>
<tr>
<td>Kidney</td>
<td>403,262 (2.2)</td>
<td>175,098 (1.8)</td>
</tr>
</tbody>
</table>

KIDNEY CANCER
Risk factors & primary prevention

- Smoking (x4)

@nhssmokefree

- Obesity
  - Chemical exposure
  - VHL disease (2-3%, clear cell RCC)
  - MET germline mutations (80% papillary type I RCC)
  - Familial (hereditary leiomyomatosis, etc.)
# KIDNEY CANCER

## TNM-Staging 8th Ed.

<table>
<thead>
<tr>
<th>T1a</th>
<th>≤4 cm</th>
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</thead>
<tbody>
<tr>
<td>T1b</td>
<td>4.1–7 cm</td>
</tr>
<tr>
<td>T2a</td>
<td>7.1–10 cm</td>
</tr>
<tr>
<td>T2b</td>
<td>&gt;10 cm</td>
</tr>
<tr>
<td>T3a</td>
<td>Invades perinephric or sinus fat and/or the renal vein</td>
</tr>
<tr>
<td>T3b</td>
<td>Invades the IVC below the diaphragm</td>
</tr>
<tr>
<td>T3c</td>
<td>Invades the IVC above the diaphragm</td>
</tr>
<tr>
<td>T4</td>
<td>Invades beyond Gerota’s fascia</td>
</tr>
<tr>
<td>N1</td>
<td>Involves regional lymph nodes</td>
</tr>
<tr>
<td>M1</td>
<td>Distant spread</td>
</tr>
</tbody>
</table>
# KIDNEY CANCER

## Clinical stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>T1 N0 M0</th>
<th>T1-2 N1 M0</th>
<th>T3 N\text{any} M0</th>
<th>T4 N\text{any} M0</th>
<th>T\text{any} N\text{any} M1</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>T2 N0 M0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td></td>
<td>T4 N\text{any} M0</td>
<td>T\text{any} N\text{any} M1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
KIDNEY CANCER
Prognosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>5-year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>81%</td>
</tr>
<tr>
<td>II</td>
<td>74%</td>
</tr>
<tr>
<td>III</td>
<td>53%</td>
</tr>
<tr>
<td>IV</td>
<td>8%</td>
</tr>
</tbody>
</table>

KIDNEY TUMOURS

Subtyping is critical

- Clinical behaviour
- Prognosis
- Treatment decision making
- „Renal Cell Carcinoma“ ≠ ccRCC
- Subtyping can be tricky (i.e. eosinophilic RCC, RCC NOS, familial cases)

#BCritical
Most frequent histology (60-75%)

~90% driven by mutations or hypermethylation of the VHL gene on 3p26 (sporadic ccRCC)

Pseudohypoxia via lost HIF1a degradation

Constitutively active VEGF signalling
CLEAR CELL RCC

Result of angiogenesis

Strongly hypervascular tumors
RISK CLASSIFICATION
# RENAL CELL CARCINOMA

Risk classification M1 disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk factor</th>
<th>Risk group</th>
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</thead>
<tbody>
<tr>
<td><strong>MSKCC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from initial diagnosis to</td>
<td>&lt;1 year</td>
<td>• 0 RFs: favourable</td>
</tr>
<tr>
<td>systemic treatment</td>
<td></td>
<td>• 1–2 RFs: intermediate</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>&lt;lower limit of normal range</td>
<td>• 3–5 RFs: poor</td>
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<tr>
<td>Corrected calcium</td>
<td>&gt;10 mg/dl</td>
<td></td>
</tr>
<tr>
<td><strong>Lactate dehydrogenase</strong></td>
<td>&gt;1.5 × upper limit of normal range</td>
<td></td>
</tr>
<tr>
<td>Karnofsky Performance Status</td>
<td>&lt;80%</td>
<td></td>
</tr>
<tr>
<td><strong>IMDC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from initial diagnosis to</td>
<td>&lt;1 year</td>
<td>• 0 RFs: favourable</td>
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<tr>
<td>systemic treatment</td>
<td></td>
<td>• 1–2 RFs: intermediate</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>&lt;lower limit of normal range</td>
<td>• 3–6 RFs: poor</td>
</tr>
<tr>
<td>Corrected calcium</td>
<td>&gt;upper limit of normal range</td>
<td></td>
</tr>
<tr>
<td><strong>Neutrophil count</strong></td>
<td>&gt;upper limit of normal range</td>
<td></td>
</tr>
<tr>
<td><strong>Platelet count</strong></td>
<td>&gt;upper limit of normal range</td>
<td></td>
</tr>
<tr>
<td>Karnofsky Performance Status</td>
<td>&lt;80%</td>
<td></td>
</tr>
</tbody>
</table>

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; mRCC, metastatic renal cell carcinoma; MSKCC, Memorial Sloan Kettering Cancer Center; RFs, risk factors.

RENAL CELL CARCINOMA

MSKCC risk classification


Median OS

- 0 risk factors (80 Patients, 21 Alive) 30 mos
- 1 or 2 risk factors (269 Patients, 36 Alive) 14 mos
- 3, 4, or 5 risk factors (88 Patients, 0 Alive) 5 mos
RENAL CELL CARCINOMA

IMDC risk classification

Heng et al. Lancet Oncology 2013
CLEAR CELL RCC

„Same, same – but different“

- Inflammatory reaction led to reclassification into a higher risk category of a relevant subset of patients

RENAL CELL CARCINOMA

Thus a matter of classification...

Commonly spreads to lymph nodes, lung, and bone

Prognostic role for site of metastasis

- Atypic
  - Pancreatic M1 → special entity?
  - Thyroid M1 → special entity?

- Oligometastatic (incl. Bone, Lung, Liver)
  - Better outcomes → Metastasectomy!?
  - Different disease?

- Bone M1 or liver M1 → poor prognosis
TREATMENT
RENAL CELL CARCINOMA

Principles of cancer treatment

- Surgery
- Chemo
- Radiotherapy
- Targeted therapy
TREATMENT
„LOCALISED DISEASE“
RENAL CELL CARCINOMA

Treatment localised disease (stage I / II)

RENAL CARCINOMA

Radical nephrectomy

- Only if organ-sparing approach not feasible (i.e. ≥ cT3)
- LND controversial in cN+ → adds staging information, no survival benefit
- Also for cytoreductive nephrectomy in Stage IV patients
CLEAR CELL RCC

Adjuvant therapy

- No RCT phase III data supporting use of adjuvant systemic treatment

- Conflicting trial results for TKI
  - S-TRAC  SUNITINIB vs. PLACEBO  OS immature
  - ASSURE  PAZOPANIB vs. PLACEBO  No OS benefit
  - PROTECT  SUNITINIB vs. PLACEBO  No OS benefit
  - Toxicity↑ / QoL↓ vs. uncertain clinical benefit

- Adjuvant sunitinib available for high risk patients in the US
  - pT3 tumors  N1 disease

- IO to come?! (NIVO or DURVA± TROME vs. PLACEBO)
TREATMENT
„ADVANCED DISEASE“
SURGERY
CLEAR CELL RCC
Cytoreductive nephrectomy

- Role of CN in TKI era questionable
- Still recommended for good risk patients
- Certainly no option for poor risk patients / high metastatic burden

RADIOTherapy
CLEAR CELL RCC

External Beam Radiotherapy

- Low response rates to conventional RT (i.e. 2 Gy / fraction)

  **BUT**

- High responses to high-dose-per-rate schedules

  - Stereotactic Ablative Radiotherapy (SABR) (i.e. 26 Gy / 1 fraction or 40 Gy / 5 fractions)
  - Causes break down of blood supply

  - Sufficient local control and low toxicity
  - Rarely used for primary RCC
  - Regularly used for metastases (e.g. brain, bone)
IMMUNOTHERAPY
„OLD FASHIONED“
RENAL CELL CARCINOMA

Immunotherapy

- RCC are strongly immunogenic tumors

- Historical treatment (and still in some US centers...)
  - High dose IL-2
  - High dose Interferon α2

- Provides durable responses in 10% of patients

- Extremely toxic (IL-2)
  - Massive capillary leakage, SIRS, organ failure due to cytokine storm
ANTIANGIOGENIC THERAPY
CLEAR CELL RCC

Tackling Neo-angiogenesis

Growth factor binding ↓

Growth factor signaling ↓

Extracellular compartment

Cell membrane

Cytoplasm

Cell death from nutrient / oxygen starvation

CLEAR CELL RCC

Available drugs: TKI

- Anti-VEGF tyrosine kinase inhibitors
  - Block intracellular activation of VEGF pathway
- Orally available
- Good penetration of blood-brain barrier
CLEAR CELL RCC

1st-line standard Sunitinib

- ORR 31% vs. 6%
- Unselected untreated ccRCC patients (~7% MSKCC poor risk)

CLEAR CELL RCC

TKI – First line

- Sunitinib (Sutent™)
  - 50mg caps OD, 4w on → 2w off
  - Side effects: fatigue, hand-foot syndrome, stomatitis
- Pazopanib (Votrient™)
  - 800mg OD
  - Side effects: diarrhoea, hair discoloration
- Axitinib (Inlyta™)
  - 5mg BID
  - Side effects: diarrhoea, dysphonia, fatigue
- Tivozanib (Fotivda™)
  - 1,340µg OD, 3w on → 1w off
  - Side effects: dysphonia, diarrhoea, fatigue

CLASS EFFECTS: HYPERTENSION, HYPOTHYROIDISM
IMMUNOTHERAPY
„MODERN WARFARE“
CLEAR CELL RCC

Immune checkpoint inhibitors 2019

- Anti-CTLA-4 monoclonal antibodies (Ipilimumab)
  - First generation
  - High incidence of auto-immune toxicity
  - Moderate efficacy

- Anti-PD-1 and anti-PD-L1 monoclonal antibodies (Nivolumab, Pembrolizumab, Avelumab, Atezolizumab)
  - Second generation
  - Less toxic
  - More efficient

- Combination therapy
  - Higher response rate but also toxicity
CLEAR CELL RCC

A new standard

CLEAR CELL RCC

Evolution of concepts

- 15-20% responders to PD-1i are long term responders
  - iRECIST important
  - When to stop treatment?
  - When to consider a cure of stage IV RCC?

- No measure for proper response prediction
  - Also PD-L1 negative tumours respond

- Combinations with promising results
  - PD-1i + CTLA-4i
  - PD-L1i + TKI
  - PD-L1i + VEGFi
CLEAR CELL RCC
EAU guideline 2019

<table>
<thead>
<tr>
<th>IMDC favourable risk disease</th>
<th>First-line therapy</th>
<th>Second-line therapy</th>
<th>Third-line therapy</th>
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</thead>
<tbody>
<tr>
<td>sunitinib or pazopanib</td>
<td>cabozantinib or nivolumab</td>
<td>cabozantinib or nivolumab</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IMDC intermediate and poor risk disease</th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ipilimumab/nivolumab</td>
<td>cabozantinib or VEGF-targeted therapy</td>
<td>cabozantinib or an alternative targeted therapy</td>
<td></td>
</tr>
<tr>
<td>cabozantinib, sunitinib or pazopanib*</td>
<td>VEGF targeted therapy or nivolumab</td>
<td>An alternative targeted therapy or nivolumab</td>
<td></td>
</tr>
</tbody>
</table>
NON-CLEAR CELL RCC

Limited evidence, limited options

- Papillary type I RCC
  - MET-driven
  - Consider Cabozantinib
- Papillary type II RCC
  - Consider anti-VEGFR TKI
- Chromophobe RCC
  - Consider Temsirolimus (mTORi)
- Collective duct / medullary RCC
  - Chemotherapy according to urothelial cancers
Kidney tumours comprise a bunge of different entities

Consider carefully if you need a biopsy

Challenge your pathologist

Clear Cell Renal Cell Carcinoma most common RCC subtype

ccRCC related to VHL inactivation and Pseudohypoxia

Angiogenesis very important for ccRCC growth

LN, lungs and bones common sites for metastatic spread
TAKE HOME MESSAGE II

RCC treatment

- Conventional chemo- and radiotherapy ineffective
- Organ-sparing surgery whenever possible in localised disease
- ccRCC’s Achilles’ heel: Angiogenesis and Immunogenicity
- No role for adjuvant systemic TKI
- Total resection for oligometastatic disease if feasible
- Cytoreductive nephrectomy no more in poor risk mRCC patients
- TKI still standard of care for good risk metastatic ccRCC
- TKI and PD-1i ± key to success in intermediate / poor risk ccRCC
EMUC 2019

... if you haven’t been to Vienna!