Update in the management of renal cancer

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Chairman EAU-ESTRO-ESUR-SIOG prostate cancer guidelines
Disclosures

Roche
Pfizer
Kidney Cancer

Clear Cell
VHL, TCEB1, BAP1

Papillary Type 1
MET

Chromophobe

Hybrid
FLCN

Oncocytoma

Papillary Type 2
FH

Papillary Epitheloid
TFE3, TFEB, MITF

Angiomyolipoma
TSC1, TSC2

Eosinophilic
SDHA, SDHB, SDHC, SDHD

Clear/Chromophobe
PTEN
# Overall survival

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage of RCC</th>
<th>Advanced disease at diagnosis (T3-4, N+, M+)</th>
<th>Fuhrman grade 3 or 4 [155]</th>
<th>CSS (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>clear-cell RCC</td>
<td>80-90%</td>
<td>28%</td>
<td>28.5%</td>
<td>Referent</td>
</tr>
<tr>
<td>papillary RCC</td>
<td>6-15%</td>
<td>17.6%</td>
<td>28.8%</td>
<td>0.64 - 0.85</td>
</tr>
<tr>
<td>chromophobe RCC</td>
<td>2-5%</td>
<td>16.9%</td>
<td>32.7%*</td>
<td>0.24 - 0.56</td>
</tr>
</tbody>
</table>

* The Fuhrman grading system is validated for ccRCC; but is unreliable for chRCC.

<table>
<thead>
<tr>
<th>Survival time</th>
<th>5 years (%)</th>
<th>10 years (%)</th>
<th>15 years (%)</th>
<th>20 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>clear-cell RCC</td>
<td>71 (69-73)</td>
<td>62 (60-64)</td>
<td>56 (53-58)</td>
<td>52 (49-55)</td>
</tr>
<tr>
<td>papillary RCC</td>
<td>91 (88-94)</td>
<td>86 (82-89)</td>
<td>85 (81-89)</td>
<td>83 (78-88)</td>
</tr>
<tr>
<td>chromophobe RCC</td>
<td>88 (83-94)</td>
<td>86 (80-92)</td>
<td>84 (77-91)</td>
<td>81 (72-90)</td>
</tr>
</tbody>
</table>
Adjuvant post surgery

3 published RCT:
Assure (Sutent / Sorafenib)
S-Trac (Sutent)
PROTECT (Pazopanib)
ASSURE. Results


N = 1923. median follow up: 6.6 years. 60% T3 or N1. All histology placebo / Sunitinib 50 mg/d (4 weeks / 6) / sorafenib 2×400 mg/d. 54 weeks

DFS

Primary objective

OS
S-TRAC


N = 615 clear cell. T ≥ 3 or N1
Sunitinib 50 mg/day (4 weeks / 6) - placebo: 1 year

HR investigator review: 0.8 (0.64-1.02)

Therefore ? ? ?
80% pT3 / 94% pN0
Pazopanib / placebo 1 year
800mg/d; decreased to 600 mg/d for toxicity

DFS (N = 1140)

ITT: 800 mg (N = 403)
HR: 0.69 [0.51-0.94]
Real toxicity (treatment stop: 28-44%) in trials!

Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Strength rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not offer adjuvant therapy with sorafenib, pazopanib or axitinib.</td>
<td>Strong</td>
</tr>
<tr>
<td>Do not offer adjuvant sunitinib following surgically resected high-risk clear-cell renal cell cancer.</td>
<td>Weak</td>
</tr>
</tbody>
</table>
Local relapse after RN

N = 102
From MD Anderson

SS prediction

Univariate
- pN1
- Delay LR < 1 year
- Size LR
- Pos op margin (LR)
- Hb level

Multivariate
- pN1
- Size of local relapse

Thomas et al, J Urol, 2015
Survival after LR (including M1)

<table>
<thead>
<tr>
<th>Feature</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade of primary tumour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 or 2</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2.28 (1.10–4.70)</td>
<td>0.026</td>
</tr>
<tr>
<td>4</td>
<td>3.92 (1.50–10.25)</td>
<td>0.005</td>
</tr>
<tr>
<td>Treatment of recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observation</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>Primary medical</td>
<td>0.47 (0.15–1.46)</td>
<td>0.19</td>
</tr>
<tr>
<td>Primary local</td>
<td>0.26 (0.12–0.56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Synchronous metastases at recurrence</td>
<td>1.12 (0.56–2.22)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Psutka et al, BJUI, 2016
Proposed algorithm

Kriegmair Eur Urol 2018

Systematic review

Management of local recurrence after curative therapy of localized renal cancer

After thermal ablation
- Surgical candidate?
  - Yes
    - Solitary Kidney?
      - Yes
        - Thermal ablation
      - No
        - PN possible?
          - Yes
            - PN
          - No
            - RN

After nephron-sparing surgery
- Surgical candidate?
  - Yes
    - Complete excision likely?
      - Yes
        - Surgery
      - No
        - Consider observation
  - No
    - Therapy required?
      - Yes
        - Systemic therapy
      - No
        - Systemic therapy + ERBI

After radical nephrectomy
- Surgical candidate?
  - Yes
    - Surgery
  - No
    - Consider observation
# EAU guidelines

## Summary of evidence

<table>
<thead>
<tr>
<th>Evidence Statement</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated recurrence in the local renal fossa is rare.</td>
<td>3</td>
</tr>
<tr>
<td>In the absence of adverse prognostic factors such as sarcomatoid features or median time interval of &lt; 12 months since treatment of the primary tumour, resection of local recurrences can induce durable tumour local control.</td>
<td>3</td>
</tr>
<tr>
<td>Most local recurrences develop within the first two years following treatment of the primary tumour. A guideline adapted follow-up regimen is advised for early detection.</td>
<td>3</td>
</tr>
</tbody>
</table>

## Recommendation

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer surgical resection of locally recurrent disease when a complete resection is possible and significant comorbidities are absent.</td>
<td>Weak</td>
</tr>
</tbody>
</table>
# M1 Prognostic Classifications

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS &lt; 80%</td>
<td>Good (0)</td>
</tr>
<tr>
<td>LDH &gt; 1.5 × ULN</td>
<td>3-year OS, 31%</td>
</tr>
<tr>
<td>Hemoglobin &lt; LLN</td>
<td>Intermediate (1–2)</td>
</tr>
<tr>
<td>Corrected calcium &gt; 10 mg/dL</td>
<td>3-year OS, 7%</td>
</tr>
<tr>
<td>Absence of nephrectomy</td>
<td>Poor (&gt; 2)</td>
</tr>
<tr>
<td></td>
<td>3-year OS, 0%</td>
</tr>
</tbody>
</table>
M1: Prognostic groups and TKI: IMDC

N = 645 treated with TKI
Heng J Clin Oncol 2009
Median survival: 22 months

Predictive factors (multivariate)
ECOG (< 80)
Delay / diagnosis (1 year)
Hb (< N°)
Corrected Calcemia (> N°)
Neutrophiles (> N°)
Platelets (> N°)

3 groups
Good: 0 facteur
Intermediate: 1 / 2
Poor > 2 factors
Initial nephrectomy in M1: Phase III

ITT analysis Flanigan J Urol 2004

With INFα

OR: 6.9% / 5.7%
  SWOG: 3.2%
  EORTC: 16%

Median survival: 13.6 / 7.8 months
Initial nephrectomy (M1): Carmena

Mejean N Engl J Med 2018
Only PS 0-1
Intermediate / high risk MSKCC
PS < 80 - LDH ≥ 1.5 x N° - Hb < lower N° limit - Corrected Calcium > 2.5 mmol/l
Diagnostic to mets < 1 year

<table>
<thead>
<tr>
<th></th>
<th>nephrectomy</th>
<th>No nephrect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate: 1-2 factors</td>
<td>55.6%</td>
<td>58.5%</td>
</tr>
<tr>
<td>Poor risk &gt; 2 factors</td>
<td>44.4%</td>
<td>41.5%</td>
</tr>
</tbody>
</table>

Non inferiority trial.
Expected: 576. Early closure: N = 450
Initial nephrectomy (M1): Carmena

Median follow up: 50.9 months

OS: 0.89 (0.71-1.10)
Non inferiority boundary: 1.2

Median survival: 18.4 months (Su)
13.9 months (surgery + Su)
EORTC trial: SURTIME

*JAMA Oncol* 2019

N = 458 expected / 99 included

Main question: immediate / deferred nephrectomy

Median follow up: 3.3 years

88% MSKCC intermediate risk
# EAU Guidelines

**For Clear cell only!**

**For IO: trials needed! (ongoing)**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not perform CN in MSKCC poor-risk patients.</td>
<td>Strong</td>
</tr>
<tr>
<td>Do not perform immediate CN in MSKCC intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy with VEGFR-TKI.</td>
<td>Weak</td>
</tr>
<tr>
<td>Start sunitinib without CN in MSKCC intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy with VEGFR-TKI.</td>
<td>Weak</td>
</tr>
<tr>
<td>Discuss delayed CN in MSKCC intermediate-risk patients under VEGFR-TKI therapy who derive long-term sustained benefit and/or minimal residual metastatic burden.</td>
<td>Weak</td>
</tr>
<tr>
<td>Perform immediate CN in patients with good performance who do not require systemic therapy.</td>
<td>Weak</td>
</tr>
</tbody>
</table>

CN: cytoreductive nephrectomy

*Bex Eur Urol 2018*
Metastasectomy?

YES . . . In selected cases

Major impact on survival if complete resection
Even in multiple locations *Alt. In* Breau *Curr Opin Urol* 2010
Metastasectomy whatever the presentation?

In practice  *Breau Curr Opin Urol 2010*

**At presentation:** major risk of occult locations

Surgery ONLY if single / easy to remove / low volume

**Secondary:** surgery to systematically consider
## Summary of evidence

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</thead>
<tbody>
<tr>
<td>All included studies were retrospective non-randomised comparative studies, resulting in a high risk of bias associated with non-randomisation, attrition, and selective reporting.</td>
<td>3</td>
</tr>
<tr>
<td>With the exception of brain and possibly bone metastases, metastasectomy remains by default the only local treatment for most sites.</td>
<td>3</td>
</tr>
<tr>
<td>Retrospective comparative studies consistently point towards a benefit of complete metastasectomy in mRCC patients in terms of overall survival, cancer-specific survival and delay of systemic therapy.</td>
<td>3</td>
</tr>
<tr>
<td>Radiotherapy to bone and brain metastases from RCC can induce significant relief from local symptoms (e.g. pain).</td>
<td>3</td>
</tr>
</tbody>
</table>

## Recommendations

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<th>Recommendation</th>
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</tr>
</thead>
<tbody>
<tr>
<td>To control local symptoms, offer ablative therapy, including metastasectomy, to patients with metastatic disease and favourable disease factors and in whom complete resection is achievable.</td>
<td>Weak</td>
</tr>
<tr>
<td>Offer stereotactic radiotherapy for clinically relevant bone or brain metastases for local control and symptom relief.</td>
<td>Weak</td>
</tr>
</tbody>
</table>
HIF pathway

VHL complex disrupted

VHL protein

β domain

Mutant α domain

Bevacizumab (Antibody)

mTOR

Temsidrolimus Everolimus

VEGF

VEGFR

PDGF

PDGFR

TGF-α

EGFR

Axitinib

Pazopanib

Sunitinib

Sorafenib
Sunitinib: survival

*Motzer J Clin Oncol 2009*

N = 750 first line, **CCC**, ECOG 0/1
Sunitinib: 50mg/d (possibly down to 25 mg). 4 weeks / 6 - INFα: 9 MU 3 times / week

Pronostic: good 36% / Intermediate: 59%

**Modified regimen: 4/6 switched to 2/1** *Bracarda Ann Oncol 2016*
FIRST line

*Motzer NEJM 2013*

\[N = 1110 \text{ CCC} \]. Pazopanib 800 mg/d vs Sunitinib 50 mg/d, 4/6 w

Stop for side effects: 24% (Pazopanib) / 20% (Sunitinib)
**MET pathway**

**Met Small Molecule Inhibitors**
- Cabozantinib
- Tivantinib
- Crizotinib
- Foretinib

**Met/HGF Antibodies**
- Rilotumumab
Cabozantinib (METEOR)

RCC (clear cell) N = 658 progressive after TKI
Cabozantinib 60 mg/day vs everolimus 10 mg/day

Choueiri Lancet Oncol, 2016

Progression-Free Survival

- **Cabozantinib (N=330)**
  - Median: 7.4 mo
  - HR 0.51 (95% CI 0.41-0.62), p<0.0001

- **Everolimus (N=328)**
  - Median: 3.9 mo

OS

- **Cabozantinib (N=330)**
  - Median OS: 21.4 mo
  - No. of deaths: 198

- **Everolimus (N=328)**
  - Median OS: 17.1 mo
  - No. of deaths: 232

HR 0.70 (95% CI 0.58-0.85), P=0.0002

Motzer Brit J Cancer 2018
Anti PD-1 (Checkmate 025)

Motzer NEJM 2015

N = 821 (progressive after TKI)
Nivolumab (3 mg/kg IV / 2 weeks) vs 10mg everolimus daily

Larger benefit if poor risk
HR = 0.48 IC\textsubscript{95} : 0.32-0.70
compared to intermediate risk
HR = 0.81 IC\textsubscript{95} : 0.61-1.06
Choosing between Cabo and Nivo?

Non eligible for nivolumab use
(autoimmune disease / steroids > 10 days)

Bone mets (+/- visceral mets)?

Symptomatic lesions at risk
(not for ORR but due to risk of PD)
Anti PD-1 + CTLA-4 (Checkmate 214)

Motzer N Engl J Med 2018

N = 1096 (ITT: 3 risk groups) Good: 249 - intermediate: 425 - poor: 422

Sunitinib 50 mg/day 4/6 weeks vs
Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg/3 weeks 4 cycles, followed by Nivo 3mg /kg /2 weeks

IMDC: intermediate: 79% - Poor: 21%

Coprimary endpoints: OS, ORR, PFS

Median follow up: 25.2 months (intermediate / poor risk)

Median OS: NR / 26 months (HR: 0.63. p < 0.001)
Objective ORR: 42% / 27% (p < 0.001)
Median PFS: 11.6 / 8.4 months (not significant based on predifined threshold)
FIRST line

Anti PD-1 + CTLA-4 (Checkmate 214)

Motzer N Engl J Med 2018

PD-L1 expression
Treatment related adverse effects:
93% (Nivo-Ipi) / 97% (Sunit)
Grade 3-4: 46% (Nivo-Ipi) / 63% (Sunit)
Adverse effect leading to treatment stop: 22% (Nivo-Ipi) / 12% (Sunit)

Overall QoL
Anti PD-L1 + anti VEGFR (JAVELIN 101)

Motzer NEJM 2019
N = 886. 80% prior RN. Clear cell
Avelumab (10 mg/kg IV / 2 weeks) + Axitinib 10 mg/d vs Sunitinib 50 mg/d 4/6 weeks
IMDC fav: 19.3/20% - Intermediate: 64.1 / 65.9% - poor: 16.3 / 13.4%

Primary objective: PFS / OS for patients with if PD-L1 + [> 1%]

63% PD-L1 + (N = 560)

---

**Graph:**
- Median Progression-free Survival (95% CI)
  - Avelumab + Axitinib: 13.8 (11.1–NE) mo
  - Sunitinib: 7.2 (5.7–9.7) mo

Stratified hazard ratio for disease progression or death: 0.61
(95% CI: 0.47–0.79)
P < 0.001

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**Anti PD-L1 + anti VEGFR** *(JAVELIN 101)*

**Motzer NEJM 2019**

**Median follow up:** 11 months

**HR for death:** 0.82 (0.53-1.28, p = 0.38)

**Side effects:** same ratio in both groups: 99.5/99.3: all grade 71.2 : 71.5% G ≥ 3
Anti PD-1 + anti VEGFR (Keynote 426)

Rini NEJM 2019

N = 1062 Clear cell.
83% prior RN

Pembro (200 mgIV / 3 weeks) + Axitinib 10 mg/d vs Sunitinib 50 mg/d 4/6 weeks

IMDC fav: 31.9/30.5% - Intermediate: 55.1 / 57.3% - poor: 13/12.1%

PD-L1 > 1: 59.3 / 61.7%

Primary objective: OS / PFS

Side effects: same ratio in both groups: 98.4/99.5: all grade 75.8/ 70.6 % G ≥ 3
FIRST line

Anti PD-1 + anti VEGFR (Keynote 426)

Rini NEJM 2019

FRACTIONS

OS

PFS

Hazard ratio for death, 0.53 (95% CI, 0.38–0.74)
P < 0.0001

Hazard ratio for disease progression or death, 0.40 (95% CI, 0.35–0.44)
P = 0.001

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EAU guidelines 2019: Clear cell

**First-line therapy**
- IMDC favourable risk disease
  - sunitinib or pazopanib

**Second-line therapy**
- IMDC intermediate and poor risk disease
  - ipilimumab/nivolumab
  - cabozantinib, sunitinib or pazopanib*

**Third-line therapy**
- IMDC intermediate and poor risk disease
  - cabozantinib or nivolumab

- cabozantinib or nivolumab
  - VEGF targeted therapy or nivolumab

- An alternative targeted therapy or nivolumab

*Pazopanib: only intermediate
**EAU guidelines 2020: clear cell**

**First line**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer pembrolizumab plus axitinib to treatment-naïve patients with any IMDC risk metastatic clear-cell RCC</td>
<td>Strong</td>
</tr>
<tr>
<td>Offer ipilimumab plus nivolumab to treatment-naïve patients with IMDC intermediate- and poor-risk metastatic clear-cell RCC</td>
<td>Strong</td>
</tr>
<tr>
<td>Offer sunitinib and pazopanib to treatment-naïve patients with IMDC favourable-, intermediate-, and poor-risk metastatic clear-cell RCC who cannot receive or tolerate immune checkpoint inhibition</td>
<td>Strong</td>
</tr>
<tr>
<td>Offer cabozantinib to treatment-naïve patients with IMDC intermediate- and poor-risk metastatic clear-cell RCC who cannot receive or tolerate immune checkpoint inhibition</td>
<td>Stronga</td>
</tr>
</tbody>
</table>

**Subsequent lines**

- Standard of care
- Alternative
- Prior IO
- Prior TKI
- Nivolumab [1b]
- Cabozantinib [1b]
- Axitinib [2b]

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## EAU guidelines 2017

<table>
<thead>
<tr>
<th>RCC type</th>
<th>MSKCC risk group [356]</th>
<th>First-line</th>
<th>LE$^*$</th>
<th>Second-Line after VEGF therapy*</th>
<th>LE$^*$</th>
<th>Third-line*</th>
<th>LE$^*$</th>
<th>Later lines</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-clear cell $^\S$</td>
<td>any</td>
<td>sunitinib</td>
<td>1b$^{^\S}$</td>
<td>Any targeted agent</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

+ notion sarcomatoides
Cf Borchielini. Compte rendu ESMO 2019

B. Ljungberg (Chair), L. Albiges, K. Bensalah, A. Bex (Vice-chair), R.H. Giles (Patient Advocate), M. Hora, M.A. Kuczyk, T. Lam, L. Marconi, A.S. Merseburger, T. Powles, M. Staehler, A. Volpe
Finally

Improved survival

Nowadays: RCT with survival as primary objective

Pricing is an issue

Drugs are important... But surgery remain key

Multidisciplinary team mandatory