Is age a prognostic factor in RCC outcome?

Theo M. de Reijke MD PhD FEBU
Chairman EORTC GU group
Department of Urology
Academic Medical Center
Amsterdam
Is age a prognostic factor in RCC outcome?

- Incidence
- Incidentalomas
- Localized disease
- Advanced/metastatic disease
Renal cell cancer - Incidence

2006:

- 38,890 new cases
- 12,840 deaths
- Steady increase in the incidence rate
- 25% advanced disease at presentation

American Cancer Society 2006
Mean age of patients with renal tumors stratified by size

Kummerlin et al 2007
Factors influencing survival

- Cell type
- Fuhrman grade
- Vascular invasion
- Tumour stage
- Performance status
Clinical staging and prognosis in RCC: American Joint Committee on Cancer Criteria

**Stage I** (5-year survival: 96%)
Tumor <7 cm in greatest dimension and limited to kidney.

**Stage II** (5-year survival: 82%)
Tumor >7 cm in greatest dimension and limited to kidney.

**Stage III** (5-year survival: 64%)
Tumor in major veins, adrenal gland, or perinephric tissue (not beyond Gerota’s fascia), and/or 1 regional lymph node involved.

**Stage IV** (5-year survival: 23%)
Tumor beyond Gerota’s fascia, >1 regional lymph node involved, and/or >1 distant metastasis.

Adapted from Cohen et al.²

Linehan et al In: Cancer: Principles and Practice of Oncology 1139-1168, 2005
## Factors predicting outcome: Cell type

Cheville et al

<table>
<thead>
<tr>
<th>Type</th>
<th>n</th>
<th>%</th>
<th>% 5-yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear Cell</td>
<td>83</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Papillary</td>
<td>11</td>
<td>87</td>
<td></td>
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<tr>
<td>Chromophobe</td>
<td>4</td>
<td>87</td>
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</tr>
<tr>
<td>Collecting Duct</td>
<td>0.3</td>
<td>Poor</td>
<td></td>
</tr>
</tbody>
</table>

*Am J Surg Pathol 2003*

*Chao J Urol 2002*
Factors predicting outcome: Fuhrman grade

- Grades 1-4
- High grade = Worse prognosis
- Sarcomatoid subtypes have worse prognosis
  Median Survival 9 months

Mian et al 2002
Prognostic factors in renal cell cancer

- TNM staging
- Tumor subtypes
- Platelets, ESR, albumin
- PS
  - UCLA integrated Staging System
  - MSKCC system
  - SSIGN (Mayo)
- Molecular markers
  - CAIX, p53, vimentin, PTEN, EpCAM
- Gene expression
  - SPROUTY, TGF-β receptor II, VCAM-1
Kidney Cancer

Renal Cell Carcinoma in Adults 40 Years Old or Less: Young Age is an Independent Prognostic Factor for Cancer-Specific Survival

Kidney Cancer

Relationship between Age at Diagnosis and Clinicopathologic Features of Renal Cell Carcinoma

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard ratios (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>T stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>1.7 (1.3–2.2)</td>
<td>10^{-3}</td>
</tr>
<tr>
<td>T3</td>
<td>2.9 (2.2–3.6)</td>
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</tr>
<tr>
<td>T4</td>
<td>4.2 (2.9–6.2)</td>
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<tr>
<td>N stage</td>
<td>1.7 (1.5–1.9)</td>
<td>10^{-3}</td>
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<tr>
<td>M stage</td>
<td>4.2 (2.9–6.2)</td>
<td>10^{-3}</td>
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<tr>
<td>Fuhrman grade</td>
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<tr>
<td>G1</td>
<td>1</td>
<td>10^{-3}</td>
</tr>
<tr>
<td>G2</td>
<td>1.1 (0.9–1.5)</td>
<td></td>
</tr>
<tr>
<td>G3</td>
<td>1.8 (1.4–2.4)</td>
<td></td>
</tr>
<tr>
<td>G4</td>
<td>2.6 (1.9–3.6)</td>
<td></td>
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<tr>
<td>Symptoms at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>10^{-3}</td>
</tr>
<tr>
<td>≥1</td>
<td>1.8 (1.5–2.1)</td>
<td></td>
</tr>
<tr>
<td>Tumour size (cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6</td>
<td>1</td>
<td>0.003</td>
</tr>
<tr>
<td>≥6</td>
<td>1.5 (1.1–1.9)</td>
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<tr>
<td>Age categories</td>
<td></td>
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<tr>
<td>≤40</td>
<td>1</td>
<td>10^{-3}</td>
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<tr>
<td>40–60</td>
<td>2.3 (1.5–3.4)</td>
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<tr>
<td>60–80</td>
<td>2.6 (1.8–3.9)</td>
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</tr>
<tr>
<td>&gt;80</td>
<td>3.0 (1.7–5.1)</td>
<td></td>
</tr>
</tbody>
</table>

95% CI = 95% confidence interval.

Renal tumours at younger age:

- lower stage and grade
- favourable histological stage
Young patients have:

- more unfavourable histological features
- higher incidence of lymph node metastases
Is age a prognostic factor in RCC outcome?

- Incidence
- Incidentalomas
- Localized disease
- Advanced/metastatic disease
### Natural history of untreated renal masses

<table>
<thead>
<tr>
<th>N-lesions</th>
<th>Size at presentation</th>
<th>Duration of FUP (mos)</th>
<th>Growth rate cm/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>234</td>
<td>2.60</td>
<td>34</td>
<td>0.28</td>
</tr>
</tbody>
</table>

- Increase in diagnosis of small tumors
- Increase most notably in 65-84 yr age group
- Approximately 20% benign tumors

Jayson & Sanders *Urology* 51:203-205, 1998
Active surveillance

- Tumors <3.5 cm rarely metastasize
- Mean growth rate up to 0.36 cm per year
Nephron sparing surgery

• Less compromise of renal function
• Protects against hyperfiltration
• No increase in the risk of recurrence
  • Lee et al *J Urol* 163:730-736, 2000
• Risk of metachronous tumour in contralateral kidney (4-15%)
Nephron sparing surgery

- Open partial nephrectomy
- Laparoscopic partial nephrectomy
- Open/Laparoscopic/Percutaneous cryoablation
- Percutaneous Radiofrequency Ablation
  - Percutaneous Interstitial laser ablation
  - High Intensity Focused Ultrasound
  - Interstitial photon radiation
Is age a prognostic factor in RCC outcome?

- Incidence
- Incidentalomas
- Localized disease
- Advanced/metastatic disease
Metastatic Resection

Better
- Pulmonary
- Isolated Long Bone
- Late presenting Tail of Pancreas
- Single metachronous brain

Poor
- Nodal
- Adrenal
- Liver
- Axial Skeleton
METASTATIC RCC

POOR PROGNOSIS: 5-year survival < 10%

- Interferon alfa: 11% ORR (4.7 m), good tolerance
- Interleukin-2: 15% ORR (19 m), high toxicity
- Median OS after progression after cytokines is 12 m

Role of NEPHRECTOMY in M+ RCC still debated

Krown SE. Cancer. 1987
Muss HB. Semin Oncol. 1988
Cytoreductive surgery

Flanigan et al *J Urol* 171:1071-1076, 2004
Cytoreductive surgery at older age

- Perioperative mortality higher
- Longer surgery time
- Greater blood loss
- OS not different from younger age group

M+ Nephrectomy in the Era of TARGETED THERAPIES…

• In combination with immunotherapy, radical nephrectomy offers a definite survival advantage
• Responses of the primary to immunotherapy were scarce
• Does the same hold for the new (multi-)targeted treatments – Small molecule inhibitors ??
  - Nephrectomy first, followed by SMI
  - SMI therapy, eventually followed by salvage surgery, or as only treatment…
Older age and renal cell cancer

- Poorer PS
- Co-morbidity higher
  - Hypertension
  - CV disease
  - Diabetes
  - GI disease
**Memorial Sloan Kettering Cancer Center (MSKCC) and Cleveland Clinic Foundation (CCF) risk factor criteria for advanced RCC**

<table>
<thead>
<tr>
<th><strong>MSKCC Criteria 2002</strong></th>
<th><strong>CCF Criteria 2005</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Prognostic Factor</strong></td>
<td><strong>Prognostic Factor</strong></td>
</tr>
<tr>
<td>Karnofsky performance status</td>
<td>Time from diagnosis to treatment with IFN-α</td>
</tr>
<tr>
<td>&lt; 80</td>
<td>&lt; 12 months</td>
</tr>
<tr>
<td>Time from diagnosis to treatment with IFN-α</td>
<td>Hemoglobin</td>
</tr>
<tr>
<td>&lt; 12 months</td>
<td>&lt; Lower limit of laboratory’s reference range</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Lactate dehydrogenase</td>
</tr>
<tr>
<td>&lt; Lower limit of laboratory’s reference range</td>
<td>&gt; 1.5 x the upper limit of laboratory’s range</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>Corrected serum calcium</td>
</tr>
<tr>
<td>&gt; 1.5 x the upper limit of laboratory’s range</td>
<td>&gt; 10.0 mg/dL</td>
</tr>
<tr>
<td>Corrected serum calcium</td>
<td>Prior radiotherapy</td>
</tr>
<tr>
<td>&gt; 10.0 mg/dL</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Presence of hepatic, lung, or retroperitoneal lymph node metastases</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

Mekhail et al *J Clin Oncol* 23:832-841, 2005
<table>
<thead>
<tr>
<th>Setting</th>
<th>Therapy</th>
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</thead>
<tbody>
<tr>
<td>First-line Therapy</td>
<td>Low + Intermediate risk</td>
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<tr>
<td></td>
<td>Sunitinib</td>
</tr>
<tr>
<td></td>
<td>Bevacuzimab</td>
</tr>
<tr>
<td></td>
<td>HD IL-2</td>
</tr>
<tr>
<td>Poor risk</td>
<td>Temsirolimus</td>
</tr>
<tr>
<td>Second-line therapy</td>
<td>Prior cytokine</td>
</tr>
<tr>
<td></td>
<td>Sorafenib</td>
</tr>
<tr>
<td>Prior VEGFR</td>
<td>Phase III trials</td>
</tr>
<tr>
<td></td>
<td>In progress</td>
</tr>
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</table>
ADVANCED RCC
Targeted therapy - Evaluation

4 weeks
Sorafenib in Advanced Clear-Cell Renal-Cell Carcinoma

Bernard Escudier, M.D., Tim Eisen, M.D., Walter M. Stadler, M.D.,
Cezary Szczylik, M.D., Stéphane Ouahad, M.D., Michael Siebels, M.D.,
Sylvie Negrier, M.D., Christine Chevreau, M.D., Ewa Solsta, M.D.,
Aparna Desai, M.D., Frédéric Rolland, M.D., Tomasz Denkow, M.D.,
Thomas E. Hutson, D.O., Pharm.D., Martin Gore, M.D., Scott Freimun, M.D.,
Bryan Schwartz, M.D., Minghua Shan, Ph.D., Roriy Simantov, M.D.,
and Ronald M. Bukowski, M.D., for the TARGET Study Group*

**ABSTRACT**

- Second line mRCC
- 39% improvement in OS

*Department of Urology, Academic Medical Center Amsterdam*
Sorafenib in Advanced Clear-Cell Renal-Cell Carcinoma

- 30% aged ≥65 years
- Trend benefit in older age group
- No difference in AE’s
- HRQOL same in both age groups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio</th>
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<tbody>
<tr>
<td><strong>Ago</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td></td>
</tr>
<tr>
<td>≥65 yr</td>
<td></td>
</tr>
<tr>
<td><strong>MSKCC prognostic risk</strong></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
</tr>
<tr>
<td>Previous interleukin-2 or interferon</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td><strong>Metastasis in lung at baseline</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td><strong>Metastasis in liver at baseline</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td><strong>Time since diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;1.5yr</td>
<td></td>
</tr>
<tr>
<td>≥1.5yr</td>
<td></td>
</tr>
<tr>
<td><strong>Top enrolling countries</strong></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td></td>
</tr>
<tr>
<td>Poland</td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td></td>
</tr>
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</table>
Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma

Robert J. Motzer, M.D., Thomas E. Hutson, D.O., Phurm.D., Piotr Tomczak, M.D., M. Dore Michaelson, M.D., Ph.D., Ronald M. Bukowski, M.D., Olivier Rixe, M.D., Ph.D., Stéphane Oudard, M.D., Ph.D., Sylvie Negrier, M.D., Ph.D., Cezary Szczylik, M.D., Ph.D., Sindy T. Kim, B.S., Irian Chen, M.D., Paul W. Bycott, Dr.P.H., Charles M. Baum, M.D., Ph.D., and Robert A. Piglin, M.D.*

**ABSTRACT**

- Untreated mRCC
- PFS 11 vs 5 months

**CONCLUSIONS**

Progression-free survival was longer and response rates were higher in patients with metastatic renal-cell cancer who received sunitinib than in those receiving interferon alfa (ClinicalTrials.gov numbers, NCT00086657 and NCT00083469).
Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma

Robert J. Motzer, M.D., Thomas E. Hutson, D. O., Pharm.D., Fleur Tomczak, M.D., M. Dorr Michaelson, M.D., Ph.D., Ronald M. Bukowski, M.D., Olivier Riex, M.D., Ph.D., Stéphane Oudard, M.D., Ph.D., Sylvie Negrier, M.D., Ph.D., Cezary Szczylik, M.D., Ph.D., Sindy T. Kim, B.S., Isaac Chen, M.D., Paul W. Bycott, Dr P.H., Charles M. Baum, M.D., Ph.D., and Robert A. Figlin, M.D.

- 36% aged ≥ 65 years
- No difference between age groups
- No difference in AE’s
- Overall objective response and clinical benefit same
Temozolomide, Interferon Alfa, or Both for Advanced Renal-Cell Carcinoma

Gary Hudes, M.D., Michael Carducci, M.D., Piotr Tomczak, M.D., Janice Dutcher, M.D., Robert Figlin, M.D., Anil Kapoor, M.D., Elzbieta Staroslawska, M.D., Jeffrey Sosman, M.D., David McDermott, M.D., István Bedrogi, M.D., Zoran Kovačević, M.D., Vladimir Lisovoy, M.D., Ingo G.H. Schmid-Wolf, M.D., Olga Barbarash, M.D., Erhan Gokmen, M.D., Timothy O'Toole, M.S., Stephanie Lustgarten, M.S., Laurence Moore, M.D., Ph.D., and Robert J. Motzer, M.D., for the Global ARCC Trial

ABSTRACT

• Poor prognosis mRCC
• Survival 10.9 vs 7.3 mos

![Graph showing survival rates](image)

adverse events in the temozolomide group than in the interferon group (P=0.02).

CONCLUSIONS
As compared with interferon alfa, temozolomide improved overall survival among patients with metastatic renal-cell carcinoma and a poor prognosis. The addition of temozolomide to interferon did not improve survival. (ClinicalTrials.gov number, NCT00065465.)
## Temsirolimus, Interferon Alfa, or Both for Advanced Renal-Cell Carcinoma

Gary Hudes, M.D., Michael Carducci, M.D., Piotr Tomaszak, M.D.

### Table: Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;65 yr</td>
<td>287</td>
<td></td>
</tr>
<tr>
<td>≤65 yr</td>
<td>129</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>287</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>129</td>
<td></td>
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<tr>
<td>Initial diagnosis to randomization</td>
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<tr>
<td>&lt;1 yr</td>
<td>338</td>
<td></td>
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<tr>
<td>≥1 yr</td>
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<tr>
<td>Karnofsky performance score</td>
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<td>&gt;70</td>
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<td>Prior nephrectomy</td>
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<td>Tumor histologic type</td>
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<tr>
<td>Clear cell</td>
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<td>Other</td>
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<tr>
<td>Hemoglobin level</td>
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<tr>
<td>&lt;1x lower limit of normal</td>
<td>340</td>
<td></td>
</tr>
<tr>
<td>≥1x lower limit of normal</td>
<td>76</td>
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<tr>
<td>Lactate dehydrogenase level</td>
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<td></td>
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<tr>
<td>&lt;1.5x upper limit of normal</td>
<td>315</td>
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<tr>
<td>&gt;1.5x upper limit of normal</td>
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<tr>
<td>Corrected serum calcium level</td>
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<tr>
<td>≤10 mg/dl</td>
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</tr>
<tr>
<td>&gt;10 mg/dl</td>
<td>126</td>
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<td>Geographic area</td>
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<tr>
<td>United States</td>
<td>122</td>
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<tr>
<td>Western Europe, Canada</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>or Australia</td>
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<td></td>
</tr>
<tr>
<td>Asia-Pacific, Eastern Europe, Africa,</td>
<td>207</td>
<td></td>
</tr>
</tbody>
</table>

### Findings:
- 30% aged ≥ 65 years
- Trend for greater benefit in younger patients
- Median OS 12 vs 8.6 mos
- No difference in AE’s
B017705: study design

IFN-α2a + bevacizumab (n=327)

IFN-α2a + placebo (n=322)

RCC patients (n=649) 1:1

- Bevacizumab/placebo 10mg/kg i.v. q2w until progression
- IFN-α2a 9MIU s.c. three times/week (maximum of 52 weeks) (dose reduction allowed)
- Multinational ex-US study: 101 study sites in 18 countries
- Stratification factors: country and Motzer score

PD = progression of disease; i.v. = intravenous; s.c. = subcutaneous

P.I. Bernard Escudier
**Progression-free survival**

(Investigator assessed)

**HR = 0.63, p < 0.0001**

**Median progression-free survival:**

- **Bevacizumab + IFN = 10.2 months**
- **IFN + placebo = 5.4 months**

**Probability of being progression-free**

<table>
<thead>
<tr>
<th>Number of patients at risk</th>
<th>Time (months)</th>
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</thead>
<tbody>
<tr>
<td>IFN + placebo 322 137 59 15 0</td>
<td>IFN + placebo 322 137 59 15 0</td>
</tr>
<tr>
<td>Bevacizumab + IFN 327 196 107 18 0</td>
<td>Bevacizumab + IFN 327 196 107 18 0</td>
</tr>
</tbody>
</table>

**Escudier et al ASCO 2007**
Subgroup analysis for progression-free survival in AVOREN

<table>
<thead>
<tr>
<th>Baseline risk factor</th>
<th>Total (n)</th>
<th>HR</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>649</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>193</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>456</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>26</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>40–64</td>
<td>384</td>
<td>0.54</td>
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</tr>
<tr>
<td>≥65</td>
<td>239</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>Number of metastatic sites</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>394</td>
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</tr>
<tr>
<td>&gt;2</td>
<td>252</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>Motzer score</td>
<td></td>
<td></td>
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<tr>
<td>Favorable</td>
<td>180</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>363</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>54</td>
<td>0.81</td>
<td></td>
</tr>
</tbody>
</table>

Escudier et al ASCO 2007
CONCLUSION 1

- Incidentalomas could be part of active surveillance in older age group (20% benign)

- In small tumors nephron sparing therapy should be considered

- M+ RCC needs multimodal treatment

- When Immunotherapy is (the only) available and the patient can have it and is fit for surgery, initial nephrectomy and if possible simultaneous M+ resection is mandatory
CONCLUSION 2

• When the patient is not fit or is not a surgical candidate because of the unfavourable or too extended M+ disease, the available systemic treatment can be discussed.

• Based on the available subgroup analyses older patients should not be excluded for targeted therapy.

• Prospective studies should be undertaken in the elderly (comorbidity, co-medication, influence of toxicity on efficacy and tolerability).