Incidence

- Estimated 39000 new cases in 2006
- Estimated 13000 deaths in 2006
- Accounts for 3% of all cancers in US
- Sixth leading cause of cancer deaths
- 90% are renal cell carcinoma (RCC)-80% being clear cell type
Risk factors for RCC

- Smoking
- Environmental factors
- Occupational factors
- Life style
- Obesity
- Diuretics
- Phencetin analgesics
- End stage kidney disease on dialysis
At presentation

- Bilateral tumors: in 4%
- 33% locally advanced or metastatic disease at presentation
- 20-40% of resected patients will develop mets after surgical recurrence
- 70% are clear cell histology
- 60% sporadic RCC are associated with VHL gene defects
## Five year survival

<table>
<thead>
<tr>
<th>Stage</th>
<th>5 year survival</th>
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<tbody>
<tr>
<td>Stage I</td>
<td>95%</td>
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<tr>
<td>Stage II</td>
<td>88%</td>
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<tr>
<td>Stage III</td>
<td>59%</td>
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<td>Stage IV</td>
<td>20%</td>
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Spontaneous regressions

- Spontaneous regressions occasionally occur.
- A prospective surveillance series of 73 patients with advanced renal cell cancer demonstrated apparent temporary objective regression in five patients (7%) without nephrectomy or any therapy.
Today’s discussion Limited to Advanced renal cell carcinoma
Historical management

- Surgery
- Radical Nephrectomy: for over 4 cm tumors
- Nephron sparing (partial nephrectomy): for less than 4 cm tumors
- Open or laparoscopic
Historical management

- Immunotherapy
- Interferon (IFN-alpha)
  - Standard arm for phase III trials
  - Overall survival of 13.1 months
  - 10-20% may respond
- IL-2
  - High dose has better responses
  - Durable responses in less than 10%
  - No clear cut overall survival advantage
Historical management

- Refractory to chemotherapy
- Only 4-6% responses
- Radiation therapy is palliative of distant mets to address local issues such as bone pain or brain mets
Cytoreductive nephrectomy

- Nephrectomy in patients with synchronous distant metastases

WHY:
- Potential for spontaneous regression of distant mets (lung mets)
- Primary tumor rarely responds to systemic therapy

- Remains fairly controversial
Cytoreductive nephrectomy

- Favoring view:
- Cytoreductive nephrectomy in selected patients who will receive postoperative interferon-α may convey a modest impact on survival.
- Nephrectomy followed by IFN alpha can delay time to progression and improve overall survival (Flanigan RC et al: J Urol. 2004: 171: 1071-1076).
- Proper patient selection is important for this aggressive approach.
Cytoreductive nephrectomy

- Contrasting view:
  - “Minimal evidence suggests that nephrectomy induces regression of distant metastases; therefore, a nephrectomy performed with the hope that it will be followed by spontaneous regression of metastases is not advised”.
Surgical resection of mets

- Selected patients with solitary or a limited number of distant metastases can achieve prolonged survival with nephrectomy and surgical resection of the metastases. Even patients with brain metastases had similar results.

- The likelihood of achieving therapeutic benefit with this approach appears enhanced in patients with a long disease-free interval between the initial nephrectomy and the development of metastatic disease.
Local Therapy

- Tumor embolization,
- external-beam radiation therapy,
- and nephrectomy
- can aid in the palliation of symptoms caused by the primary tumor or related ectopic hormone production.
Newer therapies
Gene mutations in kidney cancer

- **Gene** | **Year** | **Kidney cancer type**
- VHL | 1993 | Clear cell renal cell carcinoma
- c-Met | 1997 | Hereditary papillary renal carcinoma
- BHD | 2002 | Chromophobe renal carcinoma
It takes two "hits" to turn a cell into a tumor cell, one hit on each allele. Family members who inherit the VHL gene are born with the first hit (red); later in life, the second allele may be hit as well (yellow).
VHL mutation and RCC

- Individuals with von Hippel-Lindau (VHL) disease are at increased risk of developing RCC.

- VHL gene mutations are also common in sporadic clear-cell RCC

- The VHL protein plays an important role in the regulation of cell growth and regulates hypoxia-inducible factors (HIFs)
The VHL gene

Cytogenetic Location: 3p26-p25
The VHL gene is located on the short (p) arm of chromosome 3 between positions 26 and 25.
VHL Gene

- VHL gene is a tumor suppress gene that normally help protect cell from turning cancerous.
- Normal function is to maintain low levels of Hypoxia inducible factors or HIF.
- By binding to HIF it leads to its degradation.
Regulation of hypoxia-inducible factor alpha (HIF) by the von Hippel-Lindau tumor suppressor protein (pVHL).

Under low oxygen conditions (hypoxia), HIF is stabilized and activates transcription in concert with the coactivator proteins p300 and (CBP).

Under normal oxygen conditions (normoxia), HIF is destroyed by the proteasome.

Pathways in the cell. If the pVHL complex is not functioning properly, then the levels of Hypoxia Inducible Factor (HIF) rise, which in turns allows the overproduction of Vascular Endothelial Growth Factor (VEGF) and Platelet-derived Growth Factor (PDGF) and others. These proteins send out signals to the target cell to stimulate the growth and reproduction of the cell. The signals are received by corresponding “receptors” (like VEGFR and PDGFR in this picture). In order to stop the signal from getting through, drugs may attempt to halt the signal, trap it in transit, or block the receptor. Source: W. G. Kaelin Jr., Dana-Farber Cancer Research Institute. Clin Cancer Res. 2004 Sep 15;10(18 Pt 2):6290S-5S.
VHL Gene Mutation

- When a mutation arises in VHL that either silences it or greatly decreases its activity.
- VHL mutation leads to overproduction of a transcription factor called Hypoxia inducible factors or HIF.
- This, spurs the production of growth factors such as VEGF and PDGF, both of which fuel cancer cell growth.
- RCC is a high PDGF and VEGF expressing tumor
Pathogenesis of von Hippel-Lindau disease (VHL)–associated hemangioblastoma and renal cell carcinoma.

In hemangioblastoma, biallelic VHL inactivation in a poorly defined "stromal cell" stabilizes hypoxia-inducible factor (HIF) leading to overproduction of HIF-responsive proteins.

In renal cell carcinoma, biallelic VHL inactivation in a renal tubular epithelial cell stabilizes HIF, correlating with the formation of a premalignant renal cyst. Alterations at other loci are probably required for carcinoma development.

In VHL disease, the first VHL mutation (hit) is present in the germline.

Targeting of the \textit{VHL}-hypoxia-inducible factor (HIF)-hypoxia-induced gene pathway for treatment of renal cell carcinoma.

Potential therapeutic targets of the von Hippel-Lindau tumor suppressor protein (pVHL) pathway.

Targeted therapies

- Bevacizumab
- Sunitinib (Multi kinase inhibitor)
- Sorafenib (Multi kinase inhibitor)
- Temsirolimus
Sunitinib

- Sunitinib inhibits multiple signaling pathways
- Simultaneously inhibits PDGF and VEGF receptors, which play a role in both tumor cell proliferation and angiogenesis
- Sunitinib induced tumor regression and inhibited angiogenesis and metastatic progression in preclinical studies
Sunitinib: Mechanism

Sunitinib

- Oral agent
- Multi-targeted
- In two, phase II, clinical trials of cytokine-refractory RCC:
  - 40% Combined response rate
  - Progression free survival: approximately 8.2 months
  - Median OS: 16 months
  - 2006: FDA approved for advanced RCC
  - Combinations with IFN or Bevacizumab are under study
Sunitinib

- Phase III, randomized study

- Sunitinib vs. Interferon alfa (IFN) in treatment-naïve metastatic RCC patients:
  - Sunitinib had better progression free survival (PFS) - 11 months vs. 5 months with IFN
  - Sunitinib objective response rate (ORR) — 28% vs. 5% with IFN
Sunitinib

- Standard reference therapy for untreated patients
Sunitinib side effects

- Fatigue
- Diarrhea
- Nausea
- Stomatitis
- Hypertension
- Hand foot syndrome
- Cardiac EF decline
- Fever/chills
- Myalgia
- ? hypothyroidism
Sorafenib decreases tumor cell proliferation through upstream inhibition of receptor tyrosine kinases KIT and FLT-3, as well as downstream inhibition of serine/threonine kinases in the RAF/MEK/ERK pathway.*

Sorafenib decreases angiogenesis through upstream inhibition of receptor tyrosine kinases VEGFR and PDGFR as well as serine/threonine kinases in the RAF/MEK/ERK pathway.*

Sorafenib

- Oral agent
- Multi-targeted
- Phase II trial
- Eligibility: prior systemic treatment
- 71% had tumor shrinkage or stabilization
- Better PFS than placebo group
Sorafenib

- Phase III trial (Targets trial)
- Eligibility: 1 prior systemic treatment
- Better median OS with Sorafenib than placebo group (19.3 months vs. 15.9 months)
- Stable disease 78% vs. 55%
- 2005: FDA approved for advanced RCC
- Combinations with IFN or Bevacizumab are under study
Sorafenib

- Side effects
- Diarrhea
- Skin rash
- Hand foot syndrome
- Alopecia
- Nausea
- Hypertension
Bevacizumab

- Monoclonal antibody binding to isoforms of VEGF
- Phase II trial
- 10% PR in high dose 10 mg/kg dose arm
- Longer TTP

- Side effects: hypertension, proteinuria
Temsirirolimus (TEMSR)

- mTOR may activate HIF and thus preventing degradation and increasing HIF activity
- TEMSR is mTOR inhibitor
- Phase II data
- Median survival 15 months
- PR in 11% patients
- Poor risk status patients appears to benefit the most
Bevacizumab + IFN

- Phase III trial- frontline therapy
- Reported at ASCO 2006
- BEV + IFN vs. IFN
- All patients had kidney tumor removed surgically
- Progression free survival is doubled with Bev + IFN (10.2 vs 5.4 months)
- More follow up awaited for survival data
- Side effects: more bleeding, hypertension and proteinuria

http://www.cancer.gov/clinicaltrials/results/bevacizumab-kidney0607
Temsirilimus (TEMSR, CCI 779)

- Phase III clinical trial
- TEMSR vs. IFN vs. both
- 626 patients with advanced RCC and poor prognosis
- Received no prior systemic therapy
- TEMSR significantly increased median overall survival by 49 percent compared to interferon-alpha (10.9 months vs. 7.3 months, \( P=0.0078 \)).
- The combination of TEMSR and IFN did not significantly increase overall survival when compared with IFN alone.
- Recently approved by FDA
**Temsirolimus (TEMSR) or Interferon-alpha (IFN) or the combination of TEMSR + IFN**

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<tr>
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<th>TEMSR</th>
<th>IFN</th>
<th>Both</th>
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<tbody>
<tr>
<td>Med OS months</td>
<td>10.9</td>
<td>7.3</td>
<td>8.4</td>
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<tr>
<td>OS hazard ratio</td>
<td>0.73</td>
<td>--</td>
<td>0.95</td>
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<tr>
<td>P</td>
<td>0.0069 (SS)</td>
<td>--</td>
<td>0.6912 (NS)</td>
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NCCN guidelines: RCC

- For predominant clear cell histology
- Clinical trial
- High dose IL-2 for selected patients
- Sorafenib
- Sunitinib
- Temsirolimus for poor-prognosis patients
- Bevacizumab + IFN
- Best supportive care
Conclusions:

- Based on efficacy data: As of July 2007
- Initial therapy in treatment naive pts:
  - Sunitinib (improved PFS)
  - Bevacizumab + IFN (improved PFS)
  - Sorafenib (awaiting further data)
  - TEMSR (poor prognosis patients)
  - ?IL-2
- Cytokine refractory
  - Sorafenib
  - Sunitinib
Pending questions

- Sequential targeted therapy: No data is available yet
- Adjuvant therapy: trails are in progress.
THANK YOU