Contemporary Management of Advanced Renal Cell Carcinoma

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Epidemiology of RCC

• ~39,000 new cases of kidney cancer in the United States
• ~13,000 patients will die each year
• Since 1950 there has been a 126% increase in incidence and a 36.5% increase in annual mortality

Risk Factors
- 2:1 male to female ratio
- VHL
- Chronic dialysis/cysts
- Smoking and obesity are other known risk factors

Diagnosis of RCC

- Presenting symptoms
  - Classic diagnostic triad (hematuria, pain, palpable mass) uncommon today
- RCC is a frequent incidental discovery via ultrasonography and CT scan
- 25%–30% of patients have metastases at initial presentation

Incidental Detection

“Internist’s tumor” → “Radiologist’s tumor”

Trends in Survival With RCC

Histological Classification of Epithelial Neoplasms of the Kidney

<table>
<thead>
<tr>
<th>Type</th>
<th>Clear cell</th>
<th>Papillary type 1</th>
<th>Papillary type 2</th>
<th>Chromophobe</th>
<th>Oncocytoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated mutations</td>
<td>VHL</td>
<td>c-Met</td>
<td>FH</td>
<td>BHD</td>
<td>BHD</td>
</tr>
<tr>
<td>Incidence (%)</td>
<td>75</td>
<td>5</td>
<td>10</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Locus</td>
<td>3p25</td>
<td>7q31</td>
<td>1q42</td>
<td>17p11</td>
<td>17p11</td>
</tr>
</tbody>
</table>

BHD = Birt-Hogg-Dubé; FH = fumarate hydratase; VHL = von Hippel-Lindau.

Clinical Staging and Prognosis in RCC: American Joint Committee (AJCC) on Cancer Criteria

Stage I (10-15%)
Tumor ≤7 cm (T1) in greatest dimension and limited to kidney; 5-year survival, ~95%

Stage II (40%)
Tumor >7 cm (T2) in greatest dimension and limited to kidney; 5-year survival, ~88%

Stage III (15-20%)
Tumor in major veins or adrenal gland, tumor within Gerota’s fascia (T3), or 1 regional lymph node involved (N1); 5-year survival, ~59%

Stage IV (25-35%)
Tumor beyond Gerota’s (T4) or >1 regional lymph node involved (N2); distant metastases (M1), 5-year survival, ~20%

Impact of Stage on Outcome

• An MDACC experience suggested that 25% of pT2 patients went on to develop metastases
Identifying the High Risk Patient

- Histologic subtype
  - No difference between Clear Cell, Papillary and Chromophobe\(^1\)
- Molecular markers
  - Early in the development Ki-67, p53 and CA IX have shown some promise
- Nomograms
  - Several published from UCLA-MSKCC-Mayo all with fairly good predictive capacity\(^2\)


Surgical Management of Advanced RCC

- The only treatment modality to have a meaningful impact on advanced disease
- No significant changes in staging and outcome since Robson's description 40 years ago
- Surgery alone fails in approximately 30% of patients

Robson CJJ Urol 1969;101:297-301.
Robson Staging & Outcomes

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Survival 3 year</th>
<th>Survival 5 year</th>
<th>Survival 10 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Confined to kidney</td>
<td>73</td>
<td>66</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>Perirenal fat involvement but confined to Gerota’s</td>
<td>67</td>
<td>64</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>A – RV or IVC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>B – Lymphatic</td>
<td>59</td>
<td>42</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>C – Vascular &amp; Lymphatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>A – Adjacent organs</td>
<td>25</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>B – Distant Mets</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Impact of Mets on Overall Survival in RCC Patients

Survival threatened by lymph node and distant metastases

Robson CJJ Urol 1969;101:297-301.

**Effect of LND on Outcome with Localized Disease**

- Despite the poor outcomes seen with patients with TxN1-2M0 disease, the impact of a LND is controversial.
- There is a prospective RCT being run by the EORTC looking at the effect of a standardized LND in 772 patients.
- 5 year data did not show any impact on progression or survival.
- Only 11 patients had LN metastases.

**Metastatic RCC**

- 25% - 30% present with metastases.
- 30% with localized RCC develop metastasis.
- Most dead within 2 years.
Distribution of Metastasis

<table>
<thead>
<tr>
<th>Metastatic Site</th>
<th>Solitary/Single Organ</th>
<th>Multiple Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>30</td>
<td>75</td>
</tr>
<tr>
<td>Lymph Nodes</td>
<td>24</td>
<td>64</td>
</tr>
<tr>
<td>Bone</td>
<td>15</td>
<td>43</td>
</tr>
<tr>
<td>Liver</td>
<td>5</td>
<td>41</td>
</tr>
<tr>
<td>Brain</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Adrenal (ipsilat)</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>Adrenal (contra)</td>
<td>&lt;1</td>
<td>12</td>
</tr>
</tbody>
</table>


Multidisciplinary Approach to Metastatic RCC is Optimal

UCLA 1989-1999

% Survival

P<0.05

NX + IMT

NX

IMT

0 12 24 36 48 60 72 84 96 Months

**Rationale for Cytoreductive Nephrectomy**

- Palliation
  - Pain
  - Bleeding
  - Paraneoplastic syndrome
- Improve performance status
- Primary tumor rarely responds to systemic therapy
- Enhance response to systemic therapy
- Improved survival
- Spontaneous regression

**Argument Against Cytoreductive Nephrectomy**

- Surgical morbidity/mortality significant
- Spend majority of time left recovering from surgery
- Delays initiation of systemic therapy to treat metastatic disease
- Significant disease progression during post-operative recovery period may preclude systemic therapy
Cytoreductive Nephrectomy: MDACC

No. Patients 66
Received Rx Postop 54 (82%)
Resected to NED or Refused 9 (13.5%)
Postop Death or Progression 3 (4.5%)

95% of patients eligible for or received systemic therapy at a median of 40 days post-nephrectomy


Cytoreductive Nephrectomy for Patients with Metastatic RCC: Randomized Trials

<table>
<thead>
<tr>
<th>Study Abbreviation</th>
<th>IFN + nephrectomy (n)</th>
<th>IFN (n)</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG</td>
<td></td>
<td></td>
<td>11.1</td>
</tr>
<tr>
<td></td>
<td>(n=120)</td>
<td>IFN (n=121)</td>
<td>8.1</td>
</tr>
<tr>
<td></td>
<td>(P = .05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC</td>
<td></td>
<td></td>
<td>17.0</td>
</tr>
<tr>
<td></td>
<td>IFN + nephrectomy (n=42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IFN (n=43)</td>
<td></td>
<td>7.0</td>
</tr>
<tr>
<td></td>
<td>(P = .03)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IL2 + Nephrectomy in Metastatic RCC


Laparoscopic Cytoreductive Nephrectomy: The M. D. Anderson Experience

- From 2001 – 2005, 38 of 191 (~20%) cytoreductive nephrectomies performed laparoscopically
- Operative indices
  - Median OR time 188 minutes
  - Median estimated blood loss 175 ml
  - 3 pts (8%) electively converted
  - 2 pts (5%) major complications
  - No deaths
  - Length of stay 3.5 days
- 97% were eligible for or received systemic therapy at a median of 41 days
- Median survival 18 months

MDACC Experience with Cytoreductive Nephrectomy in the Elderly

- Given the increasing number of elderly patients aged 75 years and older presenting to urologists with metastatic RCC and the difficult management decisions, we sought to determine if outcomes were different in elderly patients as compared to a younger cohort.

Patient & Perioperative Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Elderly N=24</th>
<th>Younger N=380</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>77.5 (75-84)</td>
<td>57 (14-74)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ECOG PS - 0</td>
<td>12 (50.0)</td>
<td>219 (57.6)</td>
<td></td>
</tr>
<tr>
<td>- 1</td>
<td>11 (45.8)</td>
<td>157 (41.3)</td>
<td></td>
</tr>
<tr>
<td>- 2</td>
<td>1 (4.2)</td>
<td>4 (1.0)</td>
<td>0.29</td>
</tr>
<tr>
<td>Length of Stay (d)</td>
<td>6.0 (2-14)</td>
<td>6.0 (1-56)</td>
<td>0.18</td>
</tr>
<tr>
<td>Time to Therapy (d)</td>
<td>30.5 (10-97)</td>
<td>36.0 (7-152)</td>
<td>0.09</td>
</tr>
<tr>
<td>Survival Time (m)</td>
<td>16.6 (0-115)</td>
<td>13.7 (.3-111.3)</td>
<td>0.61</td>
</tr>
</tbody>
</table>
Survival Curves Comparing Younger to Older Cytoreductive Nephrectomy Patients

Kader et al. J. Urol. in press

RPLND In Patients With Metastatic Conventional RCC: MDACC Experience

1990 – 2005 MDACC
352  T_{any} N_{0} M_{1}
77  T_{any} N_{1-2} M_{1}

*All Conventional Histology

Median DSS
N_{0} M_{1}: 24.6 mos
N_{1-2} M_{1} (resected): 16.3* mos
N_{1-2} M_{1} (not resected): 4.9^ mos
(*, ^ p < 0.00001)

Brassell S, et al., 2006 submitted
RPLND In N+M1 Conventional RCC

Absence of Sarcomatoid Histology  
\( p=0.0001 \)  
Presence of Sarcomatoid Histology  
\( p=0.708 \)

Systemic Therapy: Memorial Sloan-Kettering Risk-Factor Model for Metastatic RCC

Greater number of risk factors is associated with worse prognosis*

- 0 risk factors (164 patients, 30 alive)
- 1 or 2 risk factors (348 patients, 23 alive)
- 3, 4, or 5 risk factors (144 patients, 1 alive)

*Risk factors: no prior nephrectomy, KPS <80, low HGB, high corrected calcium, high LDH. HGB=hemoglobin; KPS=Karnofsky performance status; LDH=lactate dehydrogenase.

Cytoreductive Nephrectomy: Summary

Patient Selection Is Critical To Success:
- Favorable performance status (0-1)
- Future systemic therapy planned
- Resection of all intra-abdominal disease

Surgical Therapy of Metastatic Disease
- Role of surgery controversial
- Is morbidity and mortality acceptable?
- Response rate to systemic therapy is improving, stimulating the interest in the neoadjuvant or adjuvant approach
### Nephrectomy and Resection of Solitary Metastasis

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>5-yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middleton, 1967</td>
<td>59</td>
<td>34%</td>
</tr>
<tr>
<td>Tolia &amp; Whitmore, 1975*</td>
<td>19</td>
<td>35%</td>
</tr>
<tr>
<td>Klugo et al, 1977</td>
<td>10</td>
<td>50%</td>
</tr>
<tr>
<td>O’Dea et al, 1978</td>
<td>44</td>
<td>16%</td>
</tr>
<tr>
<td>Golimbu et al, 1986</td>
<td>21</td>
<td>33%</td>
</tr>
<tr>
<td>Kavolius et al, 1998</td>
<td>141</td>
<td>44%</td>
</tr>
</tbody>
</table>

* Improved survival associated with P0 (p = 0.002) and N0 status (p = 0.03)

### Pulmonary Metastectomy

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>5 yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilkins et al, 1961</td>
<td>16</td>
<td>31%</td>
</tr>
<tr>
<td>Skinner et al, 1971</td>
<td>20</td>
<td>25%</td>
</tr>
<tr>
<td>DeKernion et al, 1978</td>
<td>12</td>
<td>25%</td>
</tr>
<tr>
<td>Katzenstein et al, 1978</td>
<td>16</td>
<td>38 mo mean</td>
</tr>
<tr>
<td>Mountain et al, 1978</td>
<td>16</td>
<td>50%</td>
</tr>
<tr>
<td>Morrow et al, 1980</td>
<td>25</td>
<td>24%</td>
</tr>
<tr>
<td>Jett et al, 1983</td>
<td>44</td>
<td>33 mo mean</td>
</tr>
<tr>
<td>Tanguy et al, 1996</td>
<td>51</td>
<td>61% alive at 43 mo</td>
</tr>
<tr>
<td>Piltz et al, 2002*</td>
<td>105</td>
<td>43 mo median</td>
</tr>
</tbody>
</table>

* Improved survival associated with P0 (p = 0.002) and N0 status (p = 0.03)
Resection of Metastatic RCC

• 278 patients at MSKCC
• Quality of resection
  – Complete vs incomplete: 44% vs 14% 5-year survival
• Favorable features
  – DFI >12 vs ≤ 12 months: 55% vs 9%, p < 0.0001
  – Solitary vs multiple sites: 54% vs 29%, p < 0.001
  – Age < 60 years: 49% vs 35%, p < 0.05


Surgical Management of Metastatic RCC

• Cytoreductive nephrectomy
  – Improves survival of selected patients treated in a multidisciplinary fashion
• Resection of metastatic disease
  – Possible improved survival especially with single lung mets
• Combination therapy with “newer” agents may improve results
• Neoadjuvant strategy may identify candidates for surgical consolidation
Surgical Management of Metastatic RCC

Approach in a state of evolution

Systemic Therapy of Advanced RCC

- RCC is generally resistant to standard chemotherapy (response <10%)\(^1\)
- Cytokine therapy (IL-2 or IFN-\(\alpha\)) became the standard of care for metastatic RCC with response rates of approximately 15%

- However:
  - only a minority of patients experience clinical benefit
  - adverse events can be problematic
  - second-line treatment with alternative cytokines produces responses in <5% of patients

\(^1\) Yagoda A et al Semin Oncol, 22: 42-60, 1995
Systemic Therapy of Advanced RCC

A) Hormone Therapy - Medroxyprogesterone
B) Immunologic Therapy
   - Cytokine Therapy – IL2/IFN
   - Adoptive Immunotherapy – LAK
   - Tumor Vaccines - Oncophage® HSP-96
C) Chemotherapy
D) Anti-Angiogenic Therapy - Thalidomide
E) Targeted therapy - Small Molecule Kinase Inhibitors
   - Monoclonal Antibody Therapy

Targeted Therapy

• VHL pathway
  – inactivated in over 80% of sporadic clear cell RCC

• Altered pathway results in overexpression of hypoxia-inducible genes
  • increased TGF, VEGF and PDGF, stimulating angiogenesis and cellular proliferation

• Potential targets for novel treatments
**HIF-1α Pathway**

**NORMAL O₂**

- HIF-1α
- OH
- VHL
- HIF-1α
- OH

Ubiquitin Mediated Degradation

**Clear Cell RCC Targeted Therapy**

**LOW O₂**

- HIF-1α
- OH

- VEGFR
- PDGF
- TGF
- CAIX

- Bevacizumab
- Sunitinib
- Sorafenib

**VHL MUTATION**

- E3 Ligase
- OH

- HIF-1α
- OH

No HIF Degradation

Transcriptional Activation of HIF Target Genes

- VEGFR
- PDGFR
- TGF
- EGFR

- Erlotinib
- Gefitinib
- Cetuximab

- G250
Bevacizumab in Metastatic RCC: Progression-Free Survival

![Graph showing progression-free survival of patients treated with bevacizumab at different doses compared to placebo.]


Multitargeted Approaches in Metastatic RCC: Sunitinib (SU11248)

- Small-molecule receptor tyrosine kinase inhibitor
- Inhibits all VEGFRs, PDGFR-α/β, and c-KIT
- Oral administration
- Both antitumor and antiangiogenic activity
- FDA approved January 26, 2006 for treatment of advanced RCC

<table>
<thead>
<tr>
<th>Receptors</th>
<th>IC$_{50}$ nM</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGFR-1</td>
<td>15</td>
</tr>
<tr>
<td>VEGFR-2</td>
<td>10</td>
</tr>
<tr>
<td>PDGFR</td>
<td>10</td>
</tr>
<tr>
<td>c-KIT</td>
<td>10</td>
</tr>
<tr>
<td>FGFR-1</td>
<td>880</td>
</tr>
<tr>
<td>EGFR</td>
<td>8900</td>
</tr>
</tbody>
</table>
Front Line Therapy: Phase III Trial of Sunitinib vs IFN

- Randomized, open-label, international multicenter trial
- Primary end point: progression-free survival
- Secondary end points: overall survival, toxicity, and response rate
- Trial completed accrual July 2005

Sunitinib: 50 mg administered daily (Schedule 4/2)

IFN-α: (9M IU) administered TIW

1:1 Randomization
N = 730
Previously untreated patients
Only clear-cell histology

Progression-Free Survival (Independent Central Review)

Hazard Ratio = 0.415
(95% CI: 0.320–0.539)
P <0.000001

No. at Risk Sunitinib: 235
No. at Risk IFN-α: 152

Time (Months)
Progression-Free Survival Probability

Sunitinib Median: 11 months (95% CI: 10–12)
IFN-α Median: 5 months (95% CI: 4–6)
Sunitinib in Metastatic RCC

- Approved for treatment of advanced RCC
- Sunitinib is more effective than IFN for the first line treatment of metastatic RCC
- Most adverse events were mild to moderate
- Grade 3/4 toxicities were generally managed with dose interruption or reduction

Sorafenib: Mechanism of Action

- Small-molecule receptor tyrosine kinase inhibitor
- Inhibits VEGFR-2, FLT-3, c-KIT, PDGFR-β and Raf kinases
- Oral administration
- FDA approved December 20, 2005, for treatment of advanced RCC

<table>
<thead>
<tr>
<th>Receptors</th>
<th>IC_{50} nM ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGFR-2</td>
<td>90±15</td>
</tr>
<tr>
<td>Raf-1</td>
<td>6±3</td>
</tr>
<tr>
<td>Flt-3</td>
<td>58±20</td>
</tr>
<tr>
<td>c-KIT</td>
<td>68±21</td>
</tr>
<tr>
<td>FGFR1</td>
<td>580±100</td>
</tr>
<tr>
<td>EGFR</td>
<td>&gt;10,000</td>
</tr>
</tbody>
</table>

Sorafenib in Metastatic RCC: TARGET Phase III Study Design

- Primary end point: overall survival
- Secondary end points include response rates, progression free survival, safety, health-related quality of life

**Randomization**

- **Sorafenib (400 mg BID)**: n = 451
- **Placebo**: n = 452

**Eligibility Criteria**
- Unresectable and/or metastatic RCC
- Clear-cell histology
- 1 prior systemic therapy in last 8 months
- ECOG PS 0/1

**Patient Enrollment**
- n = 903*

**Overall Survival**

- Median (months): Sorafenib (n = 451) Not reached
- Median (months): Placebo (n = 452) 14.7
- Hazard ratio (S/P): 0.72
- **P = .018**

*Out of 905 patients randomized by February 15, 2005

**Effect of Sorafenib**

57 yo man with a T1 G4 Conventional RCC metastatic to LN and bone treated with neoadjuvant sorafenib followed by lap cytoreductive nephrectomy. 36 retroperitoneal lymph nodes harvested at the time of dissection.

Pre Treatment – Biopsy Showed High Grade Conventional RCC

Post Treatment – Final pathology extensive necrosis with dense inflammatory infiltrate

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**Sorafenib in Metastatic RCC: Summary**

- Approved for treatment of advanced RCC
- Most frequent adverse events leading to dose reduction (12%) are hand-foot syndrome and diarrhea
- Improved overall survival in patients compared with placebo in randomized Phase III study
Main Toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Sorafenib</th>
<th>Sunitinib</th>
<th>Avastin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>+++</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Skin</td>
<td>++</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Hand-foot</td>
<td>+++</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Hair changes</td>
<td>+ (alopecia)</td>
<td>+ (color change)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
</tbody>
</table>

mTOR Pathway

Growth Factors

extracellular membrane

PI-3K/AKT Activation

PTEN Loss

Akt

PTEN

mTOR

S6K

4EBP1

Translation

Cyclin D1 overexpression

cMyc overexpression

HIF-1α, HIF-2α overexpression

Temsirolimus
Phase III Trial of CCI-779 in Metastatic RCC

First-line therapy in metastatic RCC
N=600 (200 per arm)
Sites ~165
Mostly clear cell

Primary end point: Survival

*Stage 4 or recurrent disease
Available at: http://www.clinicaltrial.gov/ct/show/NCT00065468?order=1

CCI-779 vs. IFN: Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>IFN Arm 1</th>
<th>TEMSR Arm 2</th>
<th>TEMSR + IFN Arm 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median overall survival</td>
<td>7.3</td>
<td>10.9</td>
<td>8.4</td>
</tr>
<tr>
<td>Log-Rank p</td>
<td>0.0069</td>
<td>0.6912</td>
<td></td>
</tr>
</tbody>
</table>

Time from Randomization, Months

Arm 1: IFN
Arm 2: Temsirolimus
Arm 3: IFN + Temsirolimus
CCI-779 in Metastatic RCC: Summary

- Most frequent adverse events leading to dose reduction: rash, mucositis, nausea, malaise
- More effective than IFN as front-line therapy

Kidney Cancer

**FIRST-LINE THERAPY**
- Clinical trial (preferred)
- High dose IL-2 for selected patients (category 1)
- Sorafenib
- Bevacizumab
- IFN
- Low dose IL-2 & IFN
- Palliative RT or Metastasectomy
- Best supportive care

**SECOND-LINE THERAPY**
- Clinical trial (preferred)
- Sorafenib (category 2B)
- Sunitinib (category 2B)
- Palliative RT or Metastasectomy
- Chemotherapy (category 3): gemcitabine or docetaxel or fotemustine or cisplatin & S-FU or doxorubicin (in sanctuary only)
- Best supportive care

Relapse or Stage IV and medically or surgically unresectable

Non-clear cell histology

Predominant clear cell histology

Progression
Adjuvant Therapy for Locally Advanced Renal Cell Carcinoma: E2805

Locally Advanced RCC
1. T2N0M0  Grade 3-4
2. T3a-cN0M0
3. T4N0M0
4. TanyN1-2M0

Surgery to remove all visible disease
Pathology confirmed

RANDOMIZE

Placebo
Sorafenib 400mg BID for one year
Sunitinib 50mg for one year 4wks on/2wks off

All RCC histologies included
1332 patients (444/arm)
-80% power to detect 33% improvement in RFS

Future Directions

• Continued early detection
• Better identification of high risk patients and thus target for neoadjuvant and adjuvant therapy
• Continued development of targetted therapies
• Evaluation of these agents in the adjuvant setting, in combination strategies, and as front-line therapy for metastatic disease
Advanced RCC Summary

- Multidisciplinary approach for locally advanced disease under evaluation

- Response rates to cytokine and chemotherapy in metastatic setting low

- Paradigm shift in the therapy of metastatic RCC – targeted therapy based upon biology

Potential Improved Survival in the Future

![Graph showing potential improved survival over time with keywords: Molecular Profiling, Imaging, Radical NX, and Targeted Therapy.](image-url)
Acknowledgements

- RCC Team
  - Christopher Wood
  - Surena Matin
  - David Swanson
- Colin Dinney
- Xifeng Wu

Trends of Incidence Over Time

Age-Adjusted (1970 US Standard) Incidence Rates Per 100,000 Person-Years for Renal Cell Carcinoma by Sex, Race, and Tumor Stage at Diagnosis--SEER, 1975-1977 to 1993-1995

Surgical Management of RCC

- Surgery is the primary approach for Stage 1 and 2 RCC\(^1\)
  - Partial vs radical nephrectomy
  - Laparoscopic vs open surgery
  - Minimally invasive approaches or expectant management
- Surgical resection of locally advanced RCC (Stage 3) is associated with high recurrence\(^1\)
  - 20%–30% recur post-radical nephrectomy, usually within 3 years
  - Adjuvant therapy has not been proven to be effective in reducing risk of relapse
- Surgical resection of Stage 4 RCC is a de-bulking procedure, but improves survival in select patients


MDACC Experience with Cytoreductive Nephrectomy in the Elderly

- Western society is aging
- Furthermore, life expectancy is increasing
- The incidence of RCC increases with age and peaks in those aged 75 to 85
- There is an increase in presentation of advanced RCC
- Elderly patients with advanced malignancy are often not offered standard therapy
Nephrectomy and Resection of Solitary Metastases

<table>
<thead>
<tr>
<th>Site Resected</th>
<th>N</th>
<th>5-year Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>50</td>
<td>56%</td>
</tr>
<tr>
<td>Gland</td>
<td>11</td>
<td>63%</td>
</tr>
<tr>
<td>Skin</td>
<td>10</td>
<td>38%</td>
</tr>
<tr>
<td>Visceral</td>
<td>23</td>
<td>30%</td>
</tr>
<tr>
<td>Appendicular bone</td>
<td>27</td>
<td>18%</td>
</tr>
<tr>
<td>Brain</td>
<td>11</td>
<td>18%</td>
</tr>
<tr>
<td>Bone</td>
<td>5</td>
<td>40%</td>
</tr>
</tbody>
</table>

RECIST CRITERIA

<table>
<thead>
<tr>
<th>Best response</th>
<th>WHO change in sum of products</th>
<th>RECIST change in sum of longest diameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Disappearance; confirmed at 4 wks?</td>
<td>Disappearance; confirmed at 4 wks?</td>
</tr>
<tr>
<td>PR</td>
<td>50% decrease; confirmed at 4 wks?</td>
<td>30% decrease; confirmed at 4 wks?</td>
</tr>
<tr>
<td>SD</td>
<td>Neither PR nor PD criteria met</td>
<td>Neither PR nor PD criteria met</td>
</tr>
<tr>
<td>PD</td>
<td>25% increase; no CR, PR, or SD documented before increased disease</td>
<td>20% increase; no CR, PR, or SD documented before increased disease</td>
</tr>
</tbody>
</table>


For the Bristol-Myers Squibb (Wallingham, CT) dataset, only unconfirmed CR and PR have been used to compare best response measured in one dimension (RECIST criteria) versus best response measured in two dimensions (WHO criteria). The computer flag identifying confirmed response in this dataset could not be used in the comparison for technical reasons.