Patient Selection for Surgery in RCC with Thrombus

E. Jason Abel, M.D.
RCC with venous invasion

- Venous invasion occurs in ~10% of RCC
- Surgery more complex
  - Increased risk for morbidity
- Thrombus may be confined to renal vein or may extend into vena cava and right heart
Presenting symptoms

- Lower extremity edema
- Right-sided varicocele in men
- Pulmonary embolus
- Caput medusae
- Protein in urine
- Cardiac or lung symptoms if higher level of thrombus
- Non-functioning renal units
- Asymptomatic
74 year old male level 4 IVC thrombus

- Segmental PE on staging CT
Surgery in patients with RCC and venous thrombus

- First surgery reported in early 20th century

- Rationale:
  1. In non-metastatic patients surgery can be curative
     ▪ 45 to 70 percent of patients without metastatic disease can be cured with surgery alone
  2. Surgery may prevent thrombus extension causing hepatic or cardiac failure
RCC patients with venous thrombus who present with pulmonary embolism

- ~5% of RCC patients with thrombus
- Do patients with PE have worse outcomes?
  - Surgery may have less benefit
  - Some RCC patients with venous thrombus who present with PE may not be offered surgery

- 90 day mortality rates for patients (non-RCC) with acute pulmonary embolism 15.4%
  - Lancet 1999
Preoperative Pulmonary Embolism Does Not Predict Poor Postoperative Outcomes in Patients with Renal Cell Carcinoma and Venous Thrombus

E. Jason Abel,* Christopher G. Wood, Nathan Eickstaedt, Justin E. Fang, Patrick Kenney, Aditya Bagrodia, Ramy F. Youssef, Arthur I. Sagalowsky and Vitaly Margulis

- Collaborative effort between U Wisconsin, UTSW, MD Anderson
- 782 consecutive RCC patients with venous thrombus undergoing surgery 1/2000-1/2011
- 35 (4.4%) patients had PE diagnosed prior to surgery
No difference in perioperative (90 day) mortality in patients who presented with PE
- (2.9% with PE vs. 5.5% without PE)

After multivariate analysis:
- No difference in cancer specific survival for patients who presented with PE
- No difference in recurrence rate in 395 RCC patients without metastases who presented with PE
  - Patients with PE were not more likely to develop pulmonary metastases

Abel et al, Journal of Urology 2013
63% of N0M0 patients did not have disease recurrence after surgery.
Principles of Surgery for Level I or II Tumor Thrombus

- Early control of renal artery
- Ligation of lumbar veins
- Clamps on large veins
  - Caudal IVC
  - Cranial IVC
  - Contralateral renal vein
- Remove kidney and thrombus en bloc

Wszolek et al., 2008
Level III thrombus

- Mobilization of liver and may require:
  - Occlusion of hepatic blood supply
Level IV thrombus

- Incise pericardium from below or may require sternotomy and bypass for open heart surgery

- Increased risk for
  - bleeding
  - stroke
  - cardiac dysfunction

D'Ancona et al., 2005
RCC patients with IVC thrombus
- NEOADJUVANT TARGETED THERAPY

- >20 publications that describe shrinking tumor thrombus using targeted agents
  - Decreasing level of IVC thrombus may facilitate less invasive surgery
  - Some dramatic responses in tumor thrombus reported
NEOADJUVANT TARGETED THERAPY: Considerations

- How often does thrombus respond?
- Does the thrombus shrink enough to change the surgical approach?
  - IVC Thrombus above the hepatic veins
- Are patients able to tolerate adverse events of systemic therapy?
- Will thrombus progression cause hepatic or cardiac failure?
RCC patients with IVC thrombus treated with targeted therapies

- Cost et al, Eur Urol 2011, 25 patients
  - 28% decrease in height
  - 44% no change
  - 28% increase in height
  - One patient changed to lower thrombus level

- Bigot et al, World J Urol 2013, 14 patients
  - Few (<10%) where therapy changed surgical approach
  - 14-28% increase in thrombus height

The majority of patients with IVC thrombus should not receive neoadjuvant targeted therapy to shrink thrombus
Would certain patients benefit from neoadjuvant therapy?

- Theoretical benefit greatest in highest level thrombus
  - Avoid cardiopulmonary bypass

- Whether or not patients benefit from neoadjuvant approach depends
  - The risk of surgery
  - Metastatic disease (consider benefits of CN)
RCC with Upper IVC thrombus

- Rare – less than 1% of RCC
- Upper level thrombus associated with technically complex surgery
  - Increased risk for morbidity and early mortality
- What are the risks?
  - Lack of high quality contemporary data in patients with upper level thrombus
## MORBIDITY AND EARLY DEATH:
RCC WITH THROMBUS ABOVE DIAPHRAGM

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Perioperative outcomes RCC with IVC thrombus above the hepatic veins; a contemporary multi-center experience

- Collaboration with 4 institutions
  - Mayo clinic
  - MD Anderson
  - UT Southwestern
  - University of Wisconsin

- 162 consecutive patients with upper level IVC thrombus

- Contemporary (2000-2012)

- Outcomes
  - Complications classified by Clavien classification
  - Death within 90 days

Abel, Thompson, Margulis et al Eur Urol. 2014
Perioperative outcomes RCC with IVC thrombus above the hepatic veins; a contemporary multi-center experience

- 1/3 patients had major complication (90 days)
  - Independent preoperative predictors
    - Level 4 thrombus
    - Systemic symptoms

No differences in complication rates or perioperative mortality in patients who had cardiopulmonary bypass or circulatory arrest

Abel, Thompson, Margulis et al Eur Urol. 2014
10% mortality in 90 days
Independent preoperative predictors: ECOG PS>1 AND Albumin < LLN

Abel, Thompson, Margulis et al Eur Urol. 2014

11.8% level 4
8.7% level 3
Management of RCC with IVC thrombus above hepatic veins

Fig. 2 – Proposed treatment algorithm for patients with upper-level inferior vena cava thrombus. 
RCC = renal cell carcinoma; IVC = inferior vena cava; ECOG = Eastern Cooperative Oncology Group; PS = performance status; LLN = lower limit of normal.

Abel, Thompson, Margulis et al Eur Urol. 2014
AFTER SURGERY..

- ~50% of non-metastatic patients recur after surgery
  - RISK DIFFERENT FOR EVERY PATIENT

- Modern multicenter data has advantages when evaluating patient’s individual risk after surgery
  - Difficult to compare patients treated in 2015 with patients treated in 1980
  - Imaging for staging and surveillance has improved significantly
  - Pathologic definitions have evolved
Most prior studies use survival as outcome measures to define prognostic factors (include pts with mRCC at presentation)

- Survival endpoints can be misleading when using modern data

- Survival with mRCC has almost doubled with newer therapies over last decade
Recurrence in non-metastatic RCC is an important outcome measure

- Recurrence is more reliable vs. survival for modern data because survival has been changing
- Rarely reported (largest prior study 76 pts)
- May help identify patients at highest risk who should be enrolled in adjuvant trials
  - Failure to show benefit from adjuvant therapy may be a result of comparing heterogeneous cohorts (combining high and low risk)
Methods

- Consecutive non-metastatic RCC patients with thrombus, attempted curative surgery 2000-2012
  - University of Wisconsin
  - UT Southwestern
  - MD Anderson Cancer Center
  - Emory University
  - Indiana University

- Multivariable models were used to identify variables associated with recurrence
  - Focus on factors that were easy to compare between institutions

- Risk modeling with predictive factors - validate in larger populations
Patient demographics

- 637 total non-metastatic RCC patients with venous thrombus
- 239 (37.5%) patients progressed to metastatic disease
- Median follow-up 24.9 months (IQR 12.2-54.9)
<table>
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<th>Significant features on Multivariable analysis</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
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<tbody>
<tr>
<td><strong>Body mass index</strong></td>
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<tr>
<td>&gt; 20</td>
<td>ref</td>
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<tr>
<td>&lt; 20</td>
<td>2.66</td>
<td>1.28-5.5</td>
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<tr>
<td><strong>Perinephric fat invasion</strong></td>
<td></td>
<td></td>
<td></td>
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<td>No</td>
<td>ref</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>1.51</td>
<td>1.09-2.1</td>
<td>0.02</td>
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<tr>
<td><strong>RCC subtype</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear cell</td>
<td>ref</td>
<td></td>
<td></td>
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<tr>
<td>Non-clear cell</td>
<td>2.13</td>
<td>1.3-3.5</td>
<td>0.03</td>
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<tr>
<td><strong>Preoperative hemoglobin</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≥ 13.6 g/dl (M), 11.6 g/dl (F)</td>
<td>ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 13.6 g/dl (M), 11.6g/dl (F)</td>
<td>1.54</td>
<td>1.07-2.15</td>
<td>0.02</td>
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<tr>
<td><strong>Nuclear grade</strong></td>
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<tr>
<td>1+2</td>
<td>ref</td>
<td></td>
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<tr>
<td>4</td>
<td>1.56</td>
<td>1.12-2.15</td>
<td>0.008</td>
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<tr>
<td><strong>Thrombus level</strong></td>
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<tr>
<td>Renal vein</td>
<td>ref</td>
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<tr>
<td>Level 3</td>
<td>2.64</td>
<td>1.47-4.74</td>
<td>0.001</td>
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<tr>
<td><strong>Maximum Tumor diameter (cm)</strong></td>
<td>1.04</td>
<td>1.00-1.09</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Risk Stratification Model (N=637)

5-yr RFS

No risk factors  79%
1 risk factor  57%
2 risk factors  50%
>2 risk factors 26%

p<0.0001

Months following nephrectomy

Recurrence-free survival
Thrombus: Renal Vein Only (N=300)

5-yr RFS

- No risk factors: 80%
- 1 risk factor: 58%
- 2 risk factors: 57%
- >2 risk factors: 23%

p<0.0001
IVC Thrombus Below Hepatics (N=263)

5-yr RFS

No risk factors 77%
1 risk factor 54%
2 risk factors 51%
>2 risk factors 26%

p=0.0003
RCC with IVC thrombus update-conclusions

- RCC with venous extension increases the complexity of surgery
  - Risk for morbidity/mortality
  - May provide durable cure in non-metastatic patients

- Upfront surgery is standard of care for most patients with venous thrombus
  - Many patients who present with PE have similar outcomes to non-PE patients
Patients should be stratified for risk following surgery

- Independent predictors of recurrence in RCC with IVC tumor thrombus:
  - BMI < 20
  - Anemia
  - Perinephric fat invasion
  - Non-clear cell histology
  - Nuclear Grade
  - Thrombus level above hepatics
  - Tumor diameter
Thank you