Controversies in management: the small renal mass.

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Disclosures

• Consultant – Teleflex Medical
• Consultant – Transenterix
• Consultant – Intuitive Surgical
• 46yo healthy male with flank pain
  – Incidental renal mass

• Options?
  – Biopsy?
  – Active Surveillance?
  – Ablation?
  – Surgery?
    • Radical?
    • Partial?
Current Controversies

- Renal Mass Biopsy
- Renal function preservation
Kidney Cancer: Increasing Incidence

Age-Adjusted SEER Incidence Rates
By Cancer Site
All Ages, All Races, Both Sexes
1992–2012 (SEER 13)

Kidney Cancer: Mortality Trends

Age-Adjusted U.S. Mortality Rates
By Cancer Site
All Ages, All Races, Both Sexes
1992–2012

Rate per 100,000

Year of Death

Kidney Cancer: Stage Migration

% Stage I tumors by year

National Cancer Database Benchmark Reports
Does renal mass biopsy belong in the algorithm?


David C. Johnson,* Josip Vukina, Angela B. Smith, Anne-Marie Meyer, Stephanie B. Wheeler, Tzy-Mey Kuo, Hung-Jui Tan, Michael E. Woods,† Mathew C. Raynor,‡ Eric M. Wallen, Raj S. Pruthi and Matthew E. Nielsen§

- 82% ↑ in estimated number of BRM removed
  - 233% ↑ for mass <1cm
  - 189% ↑ for mass 1-2cm
Renal Mass Biopsy: Fact or Fiction?

- Poor accuracy/concordance
- Risk of tumor seeding
- Complication
- Risk of coexisting RCC
- Does not change outcome

- Diagnostic 85-95%,
- >90% concordance
- 7 cases reported since 1977 (<0.01%)
- Low risk (1-8%)
- Hybrid benign/malignant 0.9-2.7% (all chromophobe and onco)
- Should it?
Renal Mass Biopsy

- 90% diagnostic on first biopsy
  - 94% after 2\textsuperscript{nd} biopsy (for initial non-diagnostic)
  - 26% benign \(\rightarrow\) 60% of these “oncocytic neoplasm”

- 63% grade concordance
  - 94% when combining low (gr 1,2) and high (gr 3,4)
  - All were under-graded on biopsy
Renal Mass Biopsy

• Implementation of RMB in SRM algorithm
  – 133 patients underwent RMB and then surgery

  – Pathology risk stratification
    • Favorable – chromophobe, gr 1 ccRCC, gr 1 pap type 1
    • Intermediate – gr 2 ccRCC, gr 2 pap type 1, unspec cc/pap/onco
    • Unfavorable – all pap type 2, any gr 3 or 4, unclassified RCC

  – 91% diagnostic
    • 94% concordance with histology
    • 65% concordance with grade

Halverson et al. (J Urol 2013)
• 100% PPV $\rightarrow$ all assigned to treatment on RMB underwent tx
• 69% NPV $\rightarrow$ of 36 assigned to AS, 11 should have been assigned to tx
• 36 pts assigned to AS based on biopsy
  – 9 based on path risk category (favorable)
  – 27 based on tumor size (<2cm)
• 4 pts with unfav path on RMB

• Is size the main determinant of AS vs treatment?
Unanswered Questions

• Who should undergo biopsy?
  – All small renal masses?
    • Young or old?
  – Surgical/ablation candidates only?

• If biopsy benign, would you still follow?
  – Young vs old patient?

• What about “oncocytic neoplasm”?
  – Is surveillance OK?
AS for Oncocytoma

• 80 patients followed for >12 months (median 33 months)
  – 95% diagnosed on biopsy

• Annual growth rate avg 0.15cm
  – Baseline tumor size associated with tumor growth

• Conclusion
  – Local progression occurs
  – Growth rate low, but increases with tumor size

Richard et al. (AUA 2015)
Renal Mass Biopsy

- Current trends in utilization
Renal Mass Biopsy: Summary

- 90% diagnostic rate
- Highly concordant for malignancy
  - Not so much for grade
- No clear consensus on when to use
- Young/healthy patient → surgery
- Elderly/significant comorbid patient → surveillance
- Those in between → intervention, AS based on size, or biopsy to gauge risk?
- Highly complex SRM → at higher risk of radical, biopsy to confirm malignancy prior?
Renal Mass Biopsy: Future Directions

• Moving beyond Fuhrman grade

- Individualized gene expression profiles
- Differing indolent vs aggressive tumors (AS vs intervention)
- microRNA expression patterns

Renal Mass Biopsy: Future Directions
Preservation of renal function

• What matters?...What matters most?

• Why is it important?
Renal Function Outcomes

- CKD and increased risk of CV disease and mortality

Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization

Alan S. Go, M.D., Glenn M. Chertow, M.D., M.P.H., Dongjie Fan, M.S.P.H., Charles E. McCulloch, Ph.D., and Chi-yuan Hsu, M.D.

Go AS, et al. (NEJM 2004)
Renal Function Outcomes: Radical vs Partial

- 26% of patients had pre-existing CKD (GFR<60 mL/min)
  - Significant increase in risk of CKD after radical nephrectomy

Huang WC, et al. (Lancet Oncol 2006)
Renal Function after NSS

Factors Predicting Renal Functional Outcome After Partial Nephrectomy

Brian R. Lane,* Denise C. Babineau,* Emilio D. Poggio,* Christopher J. Weight,* Benjamin T. Larson,* Inderbir S. Gill† and Andrew C. Novick*,‡

– 1169 patients undergoing partial nephrectomy between 1999-2006 (lap and open)
  • 25% had CKD Stage 3 or greater preoperatively
  • 18% had solitary kidney
– Factors affecting nadir eGFR
  • Preop renal function
  • Age
  • Male gender
  • Solitary kidney
  • Larger tumor size
  • Longer warm ischemia time
  • Occurrence of postop complication

Lane BR, et al. (J Urol 2008)
Warm Ischemia: The Ultimate Enemy...

Every Minute Counts When the Renal Hilum Is Clamped During Partial Nephrectomy

R. Houston Thompson, Brian R. Lane, Christine M. Lohse, Bradley C. Leibovich, Amr Fergany, Igor Frank, Inderbir S. Gill, Michael L. Blute, Steven C. Campbell

- 362 patients solitary kidney
  - PN with warm ischemia
  - Mean 21 min
- ↑ risk of ARF, acute GFR<15, and GFR<30 with longer WIT
- WIT should be minimized
Warm Ischemia: The Ultimate Enemy...

Comparison of Warm Ischemia Versus No Ischemia During Partial Nephrectomy on a Solitary Kidney

R. Houston Thompson, Brian R. Lane, Christine M. Lohse, Bradley C. Leibovich, Amr Fergany, Igor Frank, Inderbir S. Gill, Steven C. Campbell, Michael L. Blute

- 458 patients solitary kidney
  - PN with warm vs no ischemia
- ↑ risk of ARF, acute GFR<15, and new GFR<30 with warm ischemia
- PN without ischemia should be used when feasible

Thompson RH, et al. (Eur Urol 2010)
“Zero Ischemia”: Truly Better...?

Zero Ischemia Anatomical Partial Nephrectomy: A Novel Approach
Inderbir S. Gill,*† Mukul B. Patil, Andre Luis de Castro Abreu, Casey Ng, Jie Cai, Andre Berger, Manuel S. Eisenberg, Masahiko Nakamoto, Osamu Ukimura, Alvin C. Goh, Duraiyah Thangathurai, Monish Aron and Mihir M. Desai‡

• 57 patients “zero ischemia” PN
  • Preop GFR 79.6
  • 4-month post op GFR 61.5
  • 21% transfusion rate

• Is it worth it?
  • 21% transfusion rate vs 20% decline in renal function?

Gill IS, et al. (J Urol 2012)
“Zero Ischemia”: Truly Better...?

- 130 patients – superselective tumor-specific vessel clamping
  - 11 solitary kidneys (8.4%)
  - 32 baseline CKD 3 (24.6%)

- 29 required transfusion (22.3%)
- 51 postop CKD 3 (39.2%)

Satkunasivam R, et al. (Eur Urol 2015)
“Zero Ischemia”: Truly Better...?

- Single surgeon comparison of techniques and renal function outcomes (818 patients)
  - Hilar clamping – 21% decrease (GFR 78 → 61)
  - Early unclamping – 12% decrease (GFR 74 → 64)
  - “zero ischemia” – 8% decrease (GFR 76 → 69)

- Post-op GFR as measured within 30 days of surgery
  - May not represent true ultimate GFR

Hung AJ, et al. (J Urol 2013)
“Zero Ischemia”: Evolution of technique

- Completely unclamped
  - Cautery and blunt dissection along tumor capsule
    - But...don’t call it “enucleation”...call it “minimal margin”
  - Less EBL
  - Lower transfusion rate (4%)
  - Similar pre and post op GFR

Robotic Unclamped “Minimal-margin” Partial Nephrectomy: Ongoing Refinement of the Anatomic Zero-ischemia Concept

Raj Satkunasivam\textsuperscript{a,1}, Sheau Mei Tsai\textsuperscript{a,1}, Sumeet Syan\textsuperscript{a}, Jean-Christophe Bernhard\textsuperscript{a}, Andre Luis de Castro Abreu\textsuperscript{a}, Sameer Chopra\textsuperscript{a}, Andre K. Berger\textsuperscript{b}, Dennis Lee\textsuperscript{a}, Andrew J. Hung\textsuperscript{a}, Jie Cai\textsuperscript{a}, Mihir M. Desai\textsuperscript{a}, Inderbir S. Gill\textsuperscript{a,∗}
Volume Preservation: Most Important...?

Comparison of Cold and Warm Ischemia During Partial Nephrectomy in 660 Solitary Kidneys Reveals Predominant Role of Nonmodifiable Factors in Determining Ultimate Renal Function

Brian R. Lane, Paul Russo, Robert G. Uzzo, Adrian V. Hernandez, Stephen A. Boorjian, R. Houston Thompson, Amr F. Fergany, Thomas E. Love and Steven C. Campbell*;†

- 660 patients undergoing PN in a solitary kidney with warm or cold ischemia
  - At least 3 months post-op
  - Ultimate renal function dependent only on % parenchyma spared and preop GFR
    - Type of ischemia or length of ischemia not significant predictors
    - Mean 45 min CIT, 22 min WIT

Lane BR, et al. (J Urol 2011)
...or is it both?
Ischemia and Volume Preservation

- 362 patients undergoing PN in solitary kidney with warm ischemia only
  - Mean 21 min WIT
  - Predictors of new-onset ultimate GFR<30
    - Preop GFR
    - % parenchyma preserved
    - WIT > 25 minutes

Thompson RH, et al. (Urology 2012)
CKD: Medical vs Surgical

Survival and Functional Stability in Chronic Kidney Disease Due to Surgical Removal of Nephrons: Importance of the New Baseline Glomerular Filtration Rate

Brian R. Lane, Sevag Demirjian, Ithaar H. Derweesh, Toshio Takagi, Zhiling Zhang, Lily Velet, Cesar E. Ercole, Amr F. Fergany, Steven C. Campbell

• 4300 patients undergoing surgery for suspected RCC
  – No CKD – preop and postop GFR>60
    • Youngest, healthiest, most likely partial nx
  – CKD-S – preop GFR>60, postop GFR<60
    • Younger, healthier, most likely radical nx
  – CKD-M/S – preop and postop GFR<60
    • Oldest, sickest, even split radical vs partial nx
CKD:
Medical vs Surgical

Increased progression of CKD for CKD-M/S
CKD: Medical vs Surgical

- Worse survival for CKD-M/S
- Similar non-renal cancer mortality for No CKD and CKD-S

Table 3 – Multivariable analysis of renal function stability and survival

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Hazard ratio (95% confidence interval)</th>
<th>p value</th>
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<th>Hazard ratio (95% confidence interval)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD-S vs no CKD</td>
<td>1.10 (0.82–1.49)</td>
<td>0.5</td>
<td>1.19 (1.02–1.40)</td>
<td>0.030</td>
<td>1.07 (0.86–1.32)</td>
<td>0.5</td>
</tr>
<tr>
<td>CKD-M/S vs no CKD</td>
<td>2.33 (1.76–3.10)</td>
<td>&lt;0.001</td>
<td>2.01 (1.73–2.33)</td>
<td>&lt;0.001</td>
<td>1.97 (1.63–2.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CKD-M/S vs CKD-S</td>
<td>2.13 (1.59–2.86)</td>
<td>&lt;0.001</td>
<td>1.69 (1.45–1.96)</td>
<td>&lt;0.001</td>
<td>1.85 (1.53–2.22)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CKD = chronic kidney disease; CKD-S = CKD due to surgical removal of nephrons; CKD-M/S = CKD due to medical and surgical causes; GFR = glomerular filtration rate.

* Adjusted for age, gender, race, hypertension, diabetes mellitus, and cardiac disease.
CKD: Medical vs Surgical

New baseline GFR matters
Renal Function Preservation: Summary

• Most important determinants of function
  – Preop GFR, parenchyma preservation
    • Assuming average warm ischemia time (30 min or less)

• Techniques to reduce warm ischemia perhaps best for patients with lower renal function
  – Zero-ischemia, selective clamping, cold ischemia
  – ...but, at expense of increased complication risk

• New baseline GFR important for risk of progression and overall mortality
Conclusions

• Partial nephrectomy is procedure of choice...
  – When technically feasible
  – Presence of solitary kidney, CKD, genetic predisposition
  – Preponderance of data supports advantage over RN

• Minimize warm ischemia time
  – Use cold ischemia if expected clamp time long (>30 min)
  – No significant benefit (yet) of selective ischemia
    • Consider in solitary kidney or CKD, when feasible

• Maximize normal kidney preservation
• Minimize complications
  – Use whatever procedure works best for you
Future Directions

• Longer follow-up of renal function
  – Stratified by ischemia time and mass size
  – Is new-onset CKD solely responsible for survival differences?

• Improvement in renal mass biopsy
  – Molecular characterization
  – Better risk stratification

• New imaging technologies
  – Functional imaging?
  – Targeted radiotracers?

• Biomarkers
  – Diagnostic – RCC or benign, high-risk vs. low-risk
  – Prognostic – risk of ischemia-induced damage, baseline renal function