The non-neoplastic kidney in renal tumors: host versus tumor-related alterations
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- Perspective on chronic kidney disease
- Impact on the renal function of unilateral nephrectomy:
  - Healthy adult kidney donors
  - Children with Wilms tumor
  - Adults with renal cortical neoplasms
- Renal cortical landscape in which renal tumors develop (host-related alterations)
- Renal cortical manifestations of renal neoplasms (tumor-related alterations)

Key words: Renal cell carcinoma, Wilms tumor, nephrectomy, chronic kidney disease

Chronic kidney disease (CKD):
Definition: the presence of any of these findings
- eGFR <60mL/min per 1.73m²
- albuminuria
- abnormal imaging study

CKD affects 1 in 9 adults and 60% of older adults have hypertension or diabetes, the two most common causes of CKD

Risk factors for renal cell carcinoma (RCC) also affect the non neoplastic kidney
- Smoking
- Industrial compounds
- End stage kidney disease (ESRD) and acquired renal cystic disease (ARCD)
- Genetic causes

Chronic kidney disease
Expectation: a substantial fraction of nephrectomies in adults should show CKD
Fact: clinical studies indicate that 25% of patients with RCC have CKD
Hope: the diagnosis of medical renal diseases in nephrectomies may affect the medical, non oncologic, management of these patients

What is the impact of nephrectomy on the contralateral kidney in the following patient groups?
- Healthy adult kidney donors
- Children with WT
- Adults with renal cortical neoplasms
Living kidney donation
1954 the 1st transplants were performed by Joseph Murray in Boston. Since the beginning concerns existed about the consequences of living with a single kidney. Over 50 years worth of clinical experience have been accrued; 25,500 LR TPs were performed in 2005

Effects on remaining kidney in living-related donors
Renal size increases 20% (see graph below)
GFR reduced 20-25%
Creatinine increases but remains in normal range in majority
BP increases but is lower in donors than age matched controls
Urinary protein increases but remains in the normal range
Longevity: Donors live longer than age matched controls
Reason: kidney donors are healthier than controls

1st Author #Pts ESRD Yrs to RF
Rosenblatt 1,195 0.33% 15.5yr
Fehrman 1,112 0.5% 20yr
Rizvi 736 0.13% 12yr

What is the impact of nephrectomy in children with WT?

What is the impact of nephrectomy adults?
Risk of renal failure with partial vs radical nephrectomy
Risk of CKD in partial versus radical nephrectomy  
[Huang, et al http/oncology.thelancet.com]

Partial nephrectomy – magnitude of GFR reduction is proportional to the % volume loss  

Partial nephrectomy in US is under utilized: 30-65% of procedures at tertiary care centers
Only 7.5 % of procedures nationwide
Summary: renal consequences of nephrectomy

- Organ donation conveys little renal risk because of the age and good health of donors.
- Less 2% of Wilms tumor develop ESRD.
- Nephrectomy in adults for RCC carries substantial risk for CKD and ESRD, especially with radical nephrectomy (approx. 20%).

What can the non neoplastic kidney in tumor nephrectomies show to forecast future ESRD or influence clinical management?

There have been two studies of medical renal diseases in tumor nephrectomy specimens:

Bijol, et. al - 40/110 cases - 36% of cases had significant diseases
- ASVD most common
- DN 2nd most common
- Only 4 “Nephropathology dxs” - CTM, IgAN, Coll gn, thin BMN

Henrikson, et. al. – 24/246 cases - 10% significant glomerular disease
- Diabetic nephropathy most common  [ASVD not analyzed]
- Only 5 “nephropathology dxs” - TM, FSGS

Bonsib - retrospective review of 55 renal neoplasms

Summary of peri-tumoral cortex tumor related changes
1. Most RCCs have a peritumoral pseudocapsule of several mms thick likely resulting from a combination of compressive atrophy, schemic injury and obstruction. Direct parenchymal invasion without a pseudocapsule is uncommon; rarely a tumor appears to grow in harmony without a pseudocapsule.
2. Lymphangiogenesis occurs within the inflamed cortex and these neolymphatics may contain tumor. The normal lymphatics parallel arteries and veins; involvement by tumor is recognized this relationship.
3. Retrograde cortical spread of RCC occurs with extensive sinus vein involvement, to be discussed at the Evening Specialty Conference tomorrow.

Host-related findings in renal cortical neoplasms

Children
- Nephrogenic rests
- Diffuse mesangial sclerosis

Adults
- Papillary adenomas
- Hypertension/vascular disease/atheroembolism
- Diabetic glomerulopathy
- Renal cystic diseases

Host-related changes in Wilms tumors

WT is cured in 90% of pts; the remaining kidney is at risk due to:
- Irradiation and chemotherapy - develops post nephrectomy
- *Contralateral neoplastic disease
• Syndromic diseases associated with WT:
  • Denys-Drash syndrome
  • WAGR syndrome
  • GU anomalies

*Exam adjacent cortex for:
  - Diffuse mesangial sclerosis
  - Nephrogenic rests

**Denys-Drash syndrome**
Autosomal recessive disease resulting from WT1 mutations (11p13) >90% cases. WT1 is a zinc-finger transcription factor that regulates renal & gonad development

Clinical triad:
  - Male pseudohermaphrodite
  - Wilms tumor
  - Glomerulopathy due to diffuse mesangial sclerosis

*Incomplete forms occur.* All WT cases need evaluation of non neoplastic cortex

**Diffuse mesangial sclerosis**
Rapidly progressive disease: renal failure develops within 2-3 years of diagnosis

Clinical forms of diffuse mesangial sclerosis
  - Non syndromic/sporadic forms are most common
  - Syndromic forms
    - **Denys-Drash syndrome:** WT1 mutations
    - Galloway-Mowat syn: t(3:16)(p14:p13.3) mutation
    - Oculorenal syndromes
    - Schimke immuno-osseous dysplasia: SMARCAL1 mutation

**Nephrogenic rests** - persistent foci of embryonal cells capable of developing into nephroblastoma their presence indicates a risk for contralateral WT. There are two types.

**Perilobar NGR**
Peripheral in renal lobe and sharply demarcated
Blastemal and tubules with scant or sclerotic stroma
Usually multifocal

**Intralobar NGR**
Random in lobe, irregular and intermingled with nephron elements
Blastema and tubules with predominance of stroma
Often unifocal

17% of patients with nephrogenic rests have syndromic disease
<table>
<thead>
<tr>
<th></th>
<th>AllPts/%</th>
<th>DDS</th>
<th>WAGR</th>
<th>GU anom</th>
<th>BWS</th>
<th>Hemi-hyper</th>
</tr>
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<tbody>
<tr>
<td>None</td>
<td>3,460/58%</td>
<td>37%</td>
<td>18%</td>
<td>44%</td>
<td>20%</td>
<td>34%</td>
</tr>
<tr>
<td>PLNR</td>
<td>1,184/20%</td>
<td>0%</td>
<td>4%</td>
<td>9%</td>
<td>35%</td>
<td>39%</td>
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<tr>
<td>ILNR</td>
<td>1,062/18%</td>
<td>59%</td>
<td>73%</td>
<td>43%</td>
<td>18%</td>
<td>17%</td>
</tr>
<tr>
<td>Both</td>
<td>248/4%</td>
<td>4%</td>
<td>5%</td>
<td>27%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5,954</td>
<td>27</td>
<td>45</td>
<td>126</td>
<td>71</td>
<td>156</td>
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</tbody>
</table>

100% 0.45% 0.8% 2.1% 1.2% 2.6%

**Host-related changes in adults**

“Non neoplastic” cortex in papillary RCC may show tubular cytologic atypia (“incipient neoplasms”) and papillary adenomas

**Glomerulosclerosis** - when is it important? This depends upon extent and type

“Normal” age-related glomerulosclerosis by decade

- 40 yr – 10% glomerulosclerosis
- 50 yr – 15% glomerulosclerosis
- 60 yr – 20% glomerulosclerosis
- 70 yr – 25% glomerulosclerosis
- 80 yr – 30% glomerulosclerosis

[Formula: Age/2 – 10 = % “normal” glomerulosclerosis]

**Patterns of glomerulosclerosis**

- Ischemic obsolescence secondary to hypertension and vascular disease and leading to global sclerosis shows a uniform pattern of collapse and a subcapsular predominance.
- Diabetic mesangial sclerosis in early cases is subtle, but obvious in advanced cases
- Focal segmental glomerulosclerosis and fibrous crescent are important to recognize

**Cystic diseases associated with malignancy**

Genetic

- ADPKD - 1:500-1,000
- Tuberous sclerosis - 1:10,000
- Von Hippel-Lindau disease - 1:35-50,00

Acquired renal cystic disease

**Dominant polycystic kidney disease and RCC**

Walters & Braasch 1st description: 1 RCC /85 cases [Surg Gynec & Obst 58: 649, 1934]

The largest series: 3 cases Keith, et al, 1994
3 cases Hemal et al, 2000.
10pts/Ubara et al, 2008 ASN

Denominator not known!

Questionnaire sent to 507 hospitals - 5,721 patients with renal cell carcinomas
233 pts - renal cystic diseases (3.9%)
- Simple cysts 72 pts
- Acquired renal cystic disease 62 pts
  - Cystic renal cell carcinoma 56 pts
  - Multilocular renal cysts 20 pts
- "Polycystic kidney disease" 3 pts (10x)
- Miscellaneous/unspecified cysts 10 pts

Intracystic proliferations/polyps are present in 24% pts; precursors to RCC? [Gregoire et al AJKD 9:27-38, 1987]

**Tuberous sclerosis complex**

Autosomal dominant disease with dysgenic lesions: kidney, brain, skin, heart, lungs retina. TSC results from a mutation of TSC1 or TSC2, tumor suppressor genes that encode for hamartin and tuberin. Renal involvement occurs in 50-80% pts:

- Angiomyolipomas
- Cysts and cystic renal disease
- Malignant renal neoplasms

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**Renal manifestations of tuberous sclerosis complex**

[Rakowski, et. al. Kidney Int. 70:1777, 2006]

<table>
<thead>
<tr>
<th></th>
<th>TSC1</th>
<th>TSC2</th>
<th>None</th>
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<tbody>
<tr>
<td># Cases</td>
<td>36</td>
<td>75</td>
<td>23</td>
</tr>
<tr>
<td>Male</td>
<td>39%</td>
<td>57%</td>
<td>48%</td>
</tr>
<tr>
<td>AML</td>
<td>22%</td>
<td>60%</td>
<td>48%</td>
</tr>
<tr>
<td>Cysts &gt;4</td>
<td>17%</td>
<td>56%</td>
<td>67%</td>
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<tr>
<td>Cancer</td>
<td>2.8%</td>
<td>2.7%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Renal malignancy in TSC includes: RCC
Epithelioid AML (1/3 are malignant).

**The contiguous gene syndrome**

TSC2 gene is adjacent to PKD1 gene on chr 16. Dual mutations affect 5% TSC2 pts and cause the CGS. Renal failure develops early from PKD (<30yrs) and patients are at increased risk of malignancy. In CGS the cysts may be distinctive and lined by large hyperplastic eosinophilic cells.
Renal cancers reported in TCS. Not all have the contiguous gene syndrome

<table>
<thead>
<tr>
<th>1st Author</th>
<th>Year</th>
<th>Age (ave.=22 yrs)</th>
<th>B/M</th>
<th>PKD</th>
<th>Metastases/died</th>
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<tr>
<td>Aoyarna</td>
<td>2007</td>
<td>21y</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Breysem</td>
<td>2006</td>
<td>6mo</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ewalt</td>
<td>1998</td>
<td>7y</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Al-Saleem</td>
<td>1998</td>
<td>7,8,21y</td>
<td>B, M</td>
<td>2/3+</td>
<td></td>
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<tr>
<td>Bjornsson</td>
<td>1996</td>
<td>19,23,34,38,49,54</td>
<td></td>
<td></td>
<td>4/6 died</td>
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<tr>
<td>Robertson</td>
<td>1996</td>
<td>5y</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Taylor</td>
<td>1989</td>
<td>15y</td>
<td>Bil</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Weinblatt</td>
<td>1987</td>
<td>14y</td>
<td>Bil</td>
<td>+</td>
<td>Mets</td>
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<tr>
<td>Ahuja</td>
<td>1986</td>
<td>34y</td>
<td>Bil</td>
<td></td>
<td>Died mets</td>
</tr>
<tr>
<td>Shapiro</td>
<td>1984</td>
<td>23y</td>
<td>Bil</td>
<td></td>
<td></td>
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<tr>
<td>Barbour</td>
<td>1978</td>
<td>28y</td>
<td>B/M</td>
<td>+</td>
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**von Hippel-Lindau disease**
Autosomal dominant disease with: renal lesions, retinal angiomas, CNS hemangioblastomas, pheochromocytomas resulting from mutation (>300) **VHL** tumor suppressor gene (chr 3p25-26)
Multiple/bilateral clear cell lined cysts in 70-80%
Multifocal/bilateral clear cell RCCs in 40-60%

**Acquired renal cystic disease and renal cell carcinoma**
Dunhill, et. al. 1st noted an association between ARCD & RCC [J Clin Pathol 30:868, 1977]. 6/14 pts with “extensive bilateral” ARCD developed RCC noted at autopsy

Incidence of ARCD is proportional to duration of dialysis[ Matson, Med 69:217, 1990]

Incidence of RCC is proportional to the duration of dialysis
ARCD 20% - 1-3 years dialysis
33% - 3-5 years dialysis
90% - 5-10 years dialysis
20% patients with ARCD have RCC [Ishikawa, Nephron 97:c11, 2004]

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study</th>
<th>#Pts</th>
<th>ARCD</th>
<th>RCC</th>
<th>CCCa</th>
<th>Pap Ca</th>
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<tbody>
<tr>
<td>Miller</td>
<td>1989</td>
<td>Autopsy</td>
<td>155</td>
<td>58%</td>
<td>2%</td>
<td></td>
<td></td>
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<tr>
<td>Gulaniker</td>
<td>1998</td>
<td>US/CT</td>
<td>206</td>
<td>31%</td>
<td>3.8%</td>
<td></td>
<td></td>
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<tr>
<td>Farivar-Mohseni</td>
<td>2005</td>
<td>US/CT</td>
<td>852</td>
<td></td>
<td>1.6%</td>
<td>43%</td>
<td>57%</td>
</tr>
<tr>
<td>Kojima</td>
<td>2006</td>
<td>US/CT</td>
<td>2024</td>
<td></td>
<td>1.7%</td>
<td></td>
<td></td>
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<tr>
<td>Denton</td>
<td>2002</td>
<td>U-neph</td>
<td>266</td>
<td>33%</td>
<td>4.2%</td>
<td>55%</td>
<td>45%</td>
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<tr>
<td>Schwarz</td>
<td>2007</td>
<td>US/neph</td>
<td>561</td>
<td>23%</td>
<td>4.8%</td>
<td>58%</td>
<td>42%</td>
</tr>
<tr>
<td>Takahashi</td>
<td>1993</td>
<td>3-4mm</td>
<td>50</td>
<td></td>
<td>8%</td>
<td></td>
<td></td>
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</table>

ESK with ARCD
Cysts range from simple to “hyperplastic”; adenomas and RCC are common.
All RCC types occur and two new type: ARCD-assoc RCC and Papillary clear cell ca

2,624 patients - ave. 11.2 years dialysis
RCC developed in 44 patients (1.7%): 35/44 had ARCD
9/44 no cysts (not all pts have ARCD!)

Genetic renal cystic diseases and cancer
<table>
<thead>
<tr>
<th>Cystic disease</th>
<th>Incid of RCC</th>
<th>Type of Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>vHL</td>
<td>40-60%</td>
<td>Clear cell ca</td>
</tr>
<tr>
<td>TSC +/- CGS</td>
<td>2-3%</td>
<td>Clear cell ca</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epithelioid AML</td>
</tr>
</tbody>
</table>
ESK +/-ARCD  
1-2.5%  All usual types 
2 new types

ADPKD  
10x increase  Multiple types

Summary: the non-neoplastic cortex

Tumor related changes
- Compressive atrophy of nephron elements +/- fibrous pseudocapsule
- Peritumoral inflammation and lymphangiogenesis
- Retrograde cortical spread of RCC

Major Host related changes
- Children  Nephrogenic rests 
  Diffuse mesangial sclerosis
- Adults   Hypertension/vascular disease 
  Diabetic glomerulopathy 
  Renal cystic diseases and ESK

Significance of chronic kidney disease
- Patients with chronic kidney disease are at substantial risk of developing ESRD
- The life expectancy of older patients with ESRD is 2.2-4.3 years, substantially less that the life expectancy of a patient with stage 1, 2 or 3 RCC.

Significance of ASVD and DN

<table>
<thead>
<tr>
<th></th>
<th>Ave age</th>
<th>Crt &gt;6mo</th>
<th>Δ crt</th>
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<tr>
<td>Normal</td>
<td>47</td>
<td>1.2</td>
<td>0.2</td>
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<tr>
<td>ASVD - all</td>
<td>63</td>
<td>2.0</td>
<td>0.6</td>
</tr>
<tr>
<td>ASVD - mod/sev</td>
<td>65</td>
<td>2.3</td>
<td>0.7</td>
</tr>
<tr>
<td>DN - all</td>
<td>67</td>
<td>2.5</td>
<td>0.9</td>
</tr>
<tr>
<td>DN- mod/sev</td>
<td>69</td>
<td>4.6</td>
<td>1.9</td>
</tr>
</tbody>
</table>

A small increase in serum creatinine reflects a large decrease in renal function

Comments
1. Identification of organ damage attributable to diabetes and ASVD may initiate medical intervention or motivate the patient and clinician to monitor treatment of these diseases
2. There is no data or study that has explored if under diagnosis of medical disease causes harm.
3. Since both diabetes and hypertension are often under treated, a diagnosis with a comment may improve medical care and reduce morbidity.

**ADASP and CAP checklists for non-neoplastic kidney findings**

**ADASP 11/2003**
Additional findings & comments:
- Cortical adenoma
- Pyelonephritis
- Cortical infarct
- Arterio/arteriolonephrosclerosis
- Other

**CAP 1/2005**
Additional pathologic findings:
- Inflammation
- Glomerular disease
- Interstitial disease
- Other

**Recommendations**
- Pathologists must perform a systematic review of major compartments, glomeruli, tubulo-interstitium and vasculature in a section furthest removed from the tumor.
- Any suspicion of a glomerular abnormality should prompt a PAS and/or silver stain and initiate consultation with a nephropathologist.
- The RPS and ISUP should craft wording to be used for comments when moderate-severe diabetic glomerulopathy and ASVD are present to provoke a clinical response.