Kidney Cancer

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Disclosures

- Philips Healthcare
- Institutional Research Agreement
- Shared patents
- Siemens Healthineers
- Institutional Research Agreement
Key Questions

What are the unmet clinical needs in kidney cancer?

Why is Radiomics important now?

How can we transform personalized medicine with radiomics in patients with kidney cancer?
Epithelial Renal Neoplasms

<table>
<thead>
<tr>
<th>Type</th>
<th>Clear Cell</th>
<th>Papillary Type 1</th>
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<th>Chromophobe</th>
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<tbody>
<tr>
<td></td>
<td>75%</td>
<td>5%</td>
<td>10%</td>
<td>5%</td>
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</tr>
</tbody>
</table>

VHL  Met  FH  BHD

Adapted from Linehan MW et al. Clin Cancer Res 2004
Incidence & Mortality in RCC

- Increased Prevalence

- 80% ‘incidentalomas’
- Earlier stages @ diagnosis
Management of Renal Masses

- Active Surveillance
- Percutaneous Ablation
- Surgery
- Other (stereotactic radiation)
Algorithm for Management

EVALUATION
- High-quality cross-sectional imaging study (CT or MRI) with and without contrast (in the presence of adequate renal function) or access contrast enhancement, exclude angiomyolipoma, upper tract masses, features, define the relevant anatomy and evaluate the status of the contralateral kidney.
- Percutaneous renal mass core biopsy with or without FNA for patients in whom it might impact management, particularly patients with clinical or radiographic findings suggestive of lymphoma, abscess or metastasis

COUNSELING
- Review the current understanding of the natural history of clinical T1 renal masses, the relative risks of benign vs. malignant pathology and the potential role of AS.
- Review the available treatment options and the attendant benefits and risks, including oncologic considerations, renal functional considerations and potential morbidities.
- Discuss the potential advantages of a nephron-sparing treatment approach in the imperative and elective settings, including the avoidance of dialysis and reduced risk of CKD with its attendant morbidity and mortality.

INDEX PATIENT 1: Healthy; Clinical T1a
STANDARD-PN: Complete surgical excision by PN is a standard of care and should be strongly considered.
STANDARD-RN: Complete surgical excision by RN is a standard of care and should be strongly considered.
OPTION-TA: Cryoablation or RFA should be discussed as less-invasive treatment options, but local tumor recurrence is more likely, measures of success are not well defined, and surgical salvage may be difficult.
OPTION-AS: AS with delayed intervention should be discussed as an option for patients wishing to avoid treatment and willing to assume oncologic risk.

INDEX PATIENT 2: Major comorbidities; Increased surgical risk; Clinical T1a
STANDARD-PN: Complete surgical excision by PN is a standard of care and should be strongly considered.
STANDARD-RN: Should be discussed as standard of care with increased risk of CKD and surgical complications in this patient.
RECOMMENDATION-TA: Cryoablation or RFA can be discussed as a treatment option which is less effective due to increased risk of local recurrence. TA may represent suboptimal management for this healthy patient.
RECOMMENDATION-AS: AS with delayed intervention can be discussed as an option in patients who want to avoid surgery and are willing to accept an increased risk of tumor progression compared to RN or PN. AS may represent suboptimal management for this healthy patient.

INDEX PATIENT 3: Healthy; Clinical T1b
STANDARD-RN: Should be discussed as standard of care for patients with a normal contralateral kidney.
STANDARD-PN: Complete surgical excision by PN should be discussed as an alternative standard of care, particularly when there is a need to preserve renal function.
RECOMMENDATION-AS: AS should be discussed as an alternative standard of care, although it can be associated with increased surgical morbidity and an increased risk of CKD in this patient.
RECOMMENDATION-TA: Cryoablation or RFA can be discussed as a treatment option which may be advantageous in this high-risk patient, acknowledging the increased risk of local tumor recurrence compared to surgical excision.

INDEX PATIENT 4: Major comorbidities; Increased surgical risk; Clinical T1b
STANDARD-RN: Should be discussed as standard of care for patients with a normal contralateral kidney.
RECOMMENDATION-AS: AS should be discussed as a recommended modality when there is a need to preserve renal function, although it can be associated with increased urologic morbidity in this patient.

T1a < 4 cm

Low Grade (ISUP 2)

T1b > 4 cm, < 7 cm

Low Grade (ISUP 2)

GUIDELINE STATEMENT KEY
1. Standard: A guideline statement is a standard if: (1) the health outcomes of the alternative interventions are sufficiently mit meaningful decisions, a unanimity about which one.
2. Recommendation: A guid a recommendation if: (1) of the alternative intervenent
What Drives Management?

- Patient condition (age, comorbidities)
- Mass characteristics (size, location)
- Interval growth
- Location (primary vs. metastatic)
- Economics (turf battles)

Patients die of metastatic RCC, not from the primary tumor.
Cystic Renal Masses

- Younger adults more cystic component (55-85%)
- Low metastatic potential
- Better prognosis

Cao et al. Arch Path Lab Med 2005
Koga et al. Urology 2000
The Bosniak Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Follow-Up</th>
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<tbody>
<tr>
<td>I</td>
<td>Simple cyst</td>
<td>No f/u</td>
</tr>
<tr>
<td>II</td>
<td>Hairline-thin septa</td>
<td>No f/u</td>
</tr>
<tr>
<td>IIF</td>
<td>Multiple thin septae (follow up)</td>
<td>6 m f/u</td>
</tr>
<tr>
<td>III</td>
<td>Minimal irregularity/thickening of enhancing wall or septa</td>
<td>Surgery</td>
</tr>
<tr>
<td>IV</td>
<td>Enhancing soft-tissue components</td>
<td>Surgery</td>
</tr>
</tbody>
</table>

Bosniak. Radiology 1986
The Bosniak Classification: Outcomes

- 312 Bosniak lesions in 286 patients
- Surg (2.4y), ablation (2.6y), surveillance (3.2)
- Malignant: BIIF (38%), BIII (40%), BIV (90%)
- 0/144 BIIF, 1/113 BIII, 1/29 BIV - metastasis
- Moderate-Severe Complications (deaths): 19% (surg), 5% (ablation), 0% (surveillance)

Smith AD et al. AJR 2015
Cystic clear cell RCC Phenotype

- Multilocular Cystic RCC
- Predominantly Cystic RCC
- RCC + Cystic Component

Metastasis?

NO → RARE? → YES
The Bosniak Classification

I  Simple cyst
II  Hairline-thin septa
IIF Multiple thin septae (follow up)
III Minimal irregularity/thickening of enhancing wall or septa
IV  Enhancing soft-tissue components
Small Solid Renal Masses

**TABLE IV. Tumor grade (Fuhrman) by size**

<table>
<thead>
<tr>
<th>Size</th>
<th>n</th>
<th>Fuhrman Grade (n)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>1 (40)</td>
<td>2 (75)</td>
<td>3 (56)</td>
<td>4 (22)</td>
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<tr>
<td>0-2</td>
<td>20</td>
<td>8</td>
<td>12</td>
<td>0</td>
<td>0</td>
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<tr>
<td>2-3</td>
<td>28</td>
<td>3 (11)</td>
<td>21</td>
<td>4 (14)</td>
<td>0</td>
</tr>
<tr>
<td>3-4</td>
<td>18</td>
<td>4 (22)</td>
<td>10</td>
<td>4 (22)</td>
<td>0</td>
</tr>
<tr>
<td>4-5</td>
<td>16</td>
<td>4 (25)</td>
<td>7</td>
<td>4 (31)</td>
<td>0</td>
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<tr>
<td>5-6</td>
<td>13</td>
<td>3 (23)</td>
<td>3</td>
<td>2 (15)</td>
<td>1 (7.6)</td>
</tr>
<tr>
<td>6-7</td>
<td>10</td>
<td>1 (10)</td>
<td>6</td>
<td>3 (30)</td>
<td>0</td>
</tr>
<tr>
<td>&gt;7</td>
<td>42</td>
<td>0</td>
<td>20</td>
<td>18 (43)</td>
<td>4 (9.5)</td>
</tr>
</tbody>
</table>

Data in parentheses are percentage of tumors for each grade at that size.

Consider Biopsy if Surveillance

100 % RCCs < 2 cm

88% RCC < 4 cm

Duchene et al. Urology 2003
Unmet Needs in Advanced RCC

- Molecular Biology
- New ‘targeted’ therapies
- Tissue-based analysis
  - Sampling (heterogeneity)
- Tumor burden characterization
Key Questions

- What are the unmet clinical needs in kidney cancer?
- Why is Radiomics important now?
- How can we transform personalized medicine with radiomics in patients with kidney cancer?
Radiomics: Why Now?

Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

Gerlinger et al. 2012
Inter-patient, Intra-tumor Heterogeneity

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<tr>
<td>WT</td>
<td>75%</td>
<td>5%</td>
<td>10%</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

VHL          Met         FH          BHD

WT          BAP1        PBRM1       BAP1/PBRM1

Courtesy Jim Brugarolas, MD. Adapted from Linehan MW et al. Clin Cancer Res 2004
Angiogenesis in Clear Cell RCC

Adapted from Brugarolas J. *N Eng J Med* 2007

Sunitinib
Sorafenib
Pazopanib
Axitinib

Bevacizumab

Temsrolimus
Everolimus

Nivolumab

Renal Cell Carcinoma: Dynamic Contrast-enhanced MR Imaging for Differentiation of Tumor Subtypes—Correlation with Pathologic Findings

Median tumor-to-cortex enhancement indexes

Sun et al. Radiology 2009
Arterial Spin Labeling (ASL)

Differences in Blood Flow among Histologic Subtypes

Peak Blood Flow

Clear cell  Papillary  Oncocytoma

Lanzman et al. *Radiology* 2013
Tumor Heterogeneity

Pathology  T2-W  3D ASL
MRI Surrogates of Tumor Angiogenesis

ASL vs Tumor Cellularity in ccRCC

ASL Perfusion correlates with Cellularity and Detects Heterogeneity within the same tumor

Diffusion Weighted imaging (DWI)

- Malignant vs Benign
  - Sensitivity 86%
  - Specificity 78%
- High vs Low Grade
  - AUC ROC 0.83

Kang et al. AJR 2015
Manenti et al. Radiol med 2008
MR Phenotype in Papillary RCC

No Difference in Prediction of Metastases ($p=0.648$)

Progression-Free Survival
NYU, BIDMC (n=128)

Independent Size Stage Grade

Rosenkrantz et al. Eur Radiology 2013
Radiogenomic Risk Score (RRS)

SPC supervised principal component risk score (259 genes)

Jamshidi et al. Radiology 2015
Radiogenomics of Clear Cell Renal Cell Carcinoma: Associations between CT Imaging Features and Mutations

VHL: well-defined tumor margins, nodular tumor enhancement, intratumoral vasculature

KDM5C, BAP1: renal vein invasion

Karlo CA et al. Radiology 2014

BAP1 associated to ill-defined margin and Ca++ <5%
MUC4 associated with exophytic growth <9%

Shinagare et al. Abdom Imaging 2015
Texture Analysis

Courtesy Jing Wang, Ph.D. Unpublished data
Which tumor carries a worse prognosis?

Histologic Heterogeneity
Targeted Tissue Procurement

Pedrosa (PI) - NIH R01CA154475
Targeted Tissue Procurement Platform for Radiomics
Oil red O - HIGH FAT

Oil red O - LOW FAT
ASL Perfusion

DCE art

Fat Fraction

T2-W

High perfusion

Early enhancement

FF 15%

FF 2%

BAP1 -

BAP1 +

Retained contrast
Genes Best Correlated to ASL

<table>
<thead>
<tr>
<th>Genes</th>
<th>Microarray</th>
<th>Q-RTPCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABI3BP</td>
<td>R=0.644 Pval=0</td>
<td>R=0.627 Pval=0</td>
</tr>
<tr>
<td>C1S</td>
<td>R=0.528 Pval=0.001</td>
<td>R=0.277 Pval=0.035</td>
</tr>
<tr>
<td>CCDC91</td>
<td>R=0.535 Pval=0.001</td>
<td>R=0.654 Pval=0</td>
</tr>
<tr>
<td>EFNA5</td>
<td>R=0.504 Pval=0.002</td>
<td>R=0.374 Pval=0.012</td>
</tr>
<tr>
<td>CLIC1</td>
<td>R=0.599 Pval=0.002</td>
<td>R=0.304 Pval=0.027</td>
</tr>
</tbody>
</table>

ASL Blood Perfusion
Comprehensive molecular characterization of clear cell renal cell carcinoma

The Cancer Genome Atlas Research Network

Worse Prognosis
Intratumoral Heterogeneity of Lipid Metabolism in ccRCC: Dixon-MRI

Unpublished data
Correlation between MRI Phenotypes and Metabolomics
Key Questions

What are the unmet clinical needs in kidney cancer?

Why is Radiomics important now?

How can we transform personalized medicine with radiomics in patients with kidney cancer?
Bench-to-Bedside (and back)

2.6x3.4 cm

2004 Cyberknife therapy

6/2008 Cyberknife therapy
## Renal Mass with IVC Thrombus

n=207

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Clear Cell</td>
<td>68%</td>
</tr>
<tr>
<td>Papillary</td>
<td>5%</td>
</tr>
<tr>
<td>Chromophobe</td>
<td>2%</td>
</tr>
<tr>
<td>Mixed</td>
<td>9%</td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>9%</td>
</tr>
<tr>
<td>Collecting Duct</td>
<td>0%</td>
</tr>
<tr>
<td>Unclassified</td>
<td>7%</td>
</tr>
</tbody>
</table>

Large Renal Mass with IVC thrombus and lung mets

Largely necrotic. IHC+ CA9, PAX8, CK7, racemase

Most consistent with clear cell RCC.

Treatment: angiogenesis inhibitors (sunitinib, bevacizumab/interferon or pazopanib).
T1 WI

Pre

Corticomедulary

Early Nephrographic

Late Nephrographic

UT Southwestern Medical Center

Median tumor cortex enhancement index

- ccRCC
- pRCC
- Chromophobe

0.35 0.42
Repeated Biopsy

- Prominent papillary architecture microcalcifications and a strong CK7 and racemase.

**Diagnosis: high-grade papillary RCC.**

**Treatment recommendation:** Temsirolimus.
“About 2/3 of the mutations that were found in single biopsies were not uniformly detectable throughout all the sampled regions of the same patient’s tumor”
Heterogeneous Response to HIF2-I

Baseline

2 Weeks

ASL (ml/100g/min)
83 yo ♂ with met RCC on Sunitinib

- Decreasing retroperitoneal LN
- Stable bone mets
- Enlarging right adrenal met
- Local treatment with SBRT
Vascular Tumor Burden as a New Quantitative CT Biomarker for Predicting Metastatic RCC Response to Antiangiogenic Therapy\(^1\)

Smith et al. Radiology 2016
Tumor Heterogeneity in the Era of Personalized Medicine

Adapted from Greaves and Maley. Nature 2012
Radiomics

Image-Based Evolutionary Taxonomy
(US, CT, PET, MRI...)

- Predict biology of renal masses (active surveillance)
- Identify most aggressive component (Biopsy)
- Improve prediction of prognosis after surgery
- Apply phenotypic characterization to select best treatment based on genetic characteristics of primary and metastatic sites (tumor heterogeneity)
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