Hereditary Syndromes in Kidney Cancer: Beyond VHL

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Disclosure

• I have no relevant financial relationship with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.

• I do not intend to discuss an unapproved or investigative use of a commercial product/device in my presentation.
Goals

1. Review the basic epidemiology of hereditary kidney cancer.
2. Describe the more common, non-VHL, hereditary kidney cancer syndromes.
3. Highlight ways to detect patients likely to have hereditary kidney cancer.
4. Discuss when to offer genetic screening for patients who potentially have hereditary kidney cancer.
5. Suggest reasonable plans for surveillance of patients with hereditary kidney cancer syndromes.
Scope of the Problem

• 55,000 new RCC diagnoses per year in the United States.
  • Hereditary RCC accounts for 5-8% of kidney cancers
    • However, this approximation may be significantly underestimated.
    • A recent pedigree analysis from Iceland suggested that nearly 60% of patients with RCC in this population had a hereditary predisposition.

Described Syndromes

• VHL – von Hippel-Lindau (VHL)
• HPRC – Hereditary Papillary Renal Cell Carcinoma (RCC)
• BHD – Birt-Hogg-Dubé
• HLRCC – Hereditary Leiomyomatosis and RCC
• SDH-RCC – Succinate Dehydrogenase kidney cancer
• TSC – Tuberous Sclerosis Complex
• Many Others
Described Syndromes

- VHL – von Hippel-Lindau (VHL) – Not the focus of this talk . . .
- HPRC – Hereditary Papillary Renal Cell Carcinoma (RCC)
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But still very important!
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• HPRC – Hereditary Papillary Renal Cell Carcinoma (RCC)
  • Autosomal Dominant (AD) with high penetrance (90% develop RCC by 80yr)
  • Although typically diagnosed at 50-70yr, an early form has been described in 20-30yr
  • Papillary renal tumors are the only phenotype associated with this syndrome
    • Patients may have bilateral and multifocal tumors of various sizes
    • Always Type 1 papillary RCC with low nuclear grade
  • Typically hypo-vascular, enhance uniformly, and grow slowly
    • CT/MR is preferable to US for screening, because US easily can miss HPRC tumors
  • MET - proto-oncogene that encodes surface receptor for hepatocyte growth factor
    • Rationale for targeted MET inhibition – 50% of those with germline MET mutations had a PR

Choueiri et al. JCO 2013
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• **BHD – Birt-Hogg-Dubé**
  • AD syndrome characterized by skin, lung, and kidney lesions
  • Fibrofolliculomas
  • Lung Lesions = Lung cysts and blebs
    • Nearly 30% experience a pneumothorax
  • Renal tumors occur in 25-35% with a wide range of onset (mean age: 50 yr)
  • Chromophobe RCCs and Hybrid Oncocytic tumors
    • ccRCC and pRCC have been reported
  • Germline mutation of FLCN
    • Folliculin - tumor-suppressor involved in the regulation of AMPK and mTOR signaling pathways
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- **HLRCC – Hereditary Leiomyomatosis and RCC**
  - AD syndrome - variant of Multiple Cutaneous and Uterine Leiomyomatosis (MCUL)
  - Uterine leiomyomas occur in >90% of women with MCUL
    - Frequently requiring a hysterectomy at <30 yr of age
  - RCC is found in approximately 20% of MCUL families with an early onset (late 30s)
  - HLRCC associated RCCs are typically solitary, unilateral, and high grade (Type 2 papillary RCC)
  - HLRCC-related RCCs are the most aggressive hereditary renal tumors
    - Most patients have died of metastatic disease within 5 yr after diagnosis regardless of primary tumor size
  - Early radical nephrectomy is indicated
  - Biallelic inactivation of *FH* gene (fumarate hydratase)
    - Kreb’s cycle affected leading to metabolic shift towards anaerobic glycolysis (Warburg effect)
    - Metabolic activity may provide rationale to stage with FDG-PET
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- **SDH-RCC** – *Succinate Dehydrogenase associated kidney cancer*
  - AD syndrome affecting SDH (Kreb’s Cycle Enzyme)
    - Germline mutations in SDH subunits B/C/D have been seen in relation to developing early RCC
    - Similar to FH mutation in HLRCC – Warburg effect and associated aggressive phenotype
  - SDH mutations associated with Hereditary Paraganglioma/Pheochromocytomas and GISTs
  - Young age of diagnosis with RCC (Median 30s-40s)
  - May represent varying subtypes of renal lesions – ccRCC, chromophobe RCC, Oncocytomas
  - Like HLRCCs, these are aggressive hereditary renal tumors = Early Surgery
    - Unlike HLRCC, there is potential development of metachronous, bilateral RCC, thus NSS should be considered
    - Because of the potential for aggressive tumors, wide surgical excision of SDH-RCC is recommended
    - Potential role for PET as with HLRCC

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- **TSC – Tuberous Sclerosis Complex**
  - 70% with a spontaneous germline mutation and 30% have an AD inherited syndrome
  - Inactivating mutations in either TSC1 (9q34, Hamartin) or TSC2 (16p13, Tuberin)
    - Hamartin and Tuberin bind together to form a functional heterodimer that inhibits downstream mTOR pathways
  - Characterized by Seizures, Facial angiofibromas, Mental retardation, SEGAs, Renal AMLs
  - Renal lesions occur in 50–80% of patients and primarily include AMLs and Cysts
    - AMLs are the most common renal lesions
  - RCC has been reported in 1–4% of TSC patients
    - Overall incidence of RCC approximates that of the general population, **BUT** occurs at a younger age (mean - 28 yr)
  - TSC-associated RCCs are principally clear cell RCC
    - RCC may be difficult to distinguish from fat-poor AML or eAML – consider biopsy as therapy would vary
  - Potential for metachronous, bilateral AMLs or RCC, thus nephron-sparing approaches encouraged
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Described Syndromes

• Others:
  • Cowden syndrome
  • MITF (microphthalmia-associated transcription factor) associated RCC
  • Hereditary hyperparathyroidism-jaw tumor syndrome
  • Papillary thyroid carcinoma with associated papillary renal neoplasia
  • Constitutional chromosome 3 translocations
  • Familial ccRCC
Detecting Patients with HRC Syndromes

• Past personal medical history
  • Dermatologic
  • Ophthalmologic
  • Pulmonary
  • Neurologic

• Family history

• Physical Exam
  • Dermatologic
  • Ophthalmologic
  • Pulmonary
  • Neurologic
Genetic Screening

• NCI Experience – compared hereditary RCC cases to SEER data
  • The median age of patients with RCC in SEER was 64 years-old
  • The bottom 10th percentile cutoff was 46 years-old
  • The median age of hereditary kidney cancer patients at the NCI = 37 years-old
    • 70% of hereditary cases found at or below the 46 year-old cut off
  • Using the 10th Percentile cut-off maximized sensitivity and specificity

Shuch et al. JCO 2013
Surveillance for those with HRC Syndromes

• **VHL**
  • Annually:
    • Physical Exam including an eye/retinal examination
    • Abdominal Ultrasound, and at least every other year Abdominal MRI scan to assess kidneys, pancreas, and adrenals
    • Plasma free metanephrines
  • Every two years:
    • MRI with and without contrast of brain, cervical, thoracic, and lumbar spine
    • Audiology assessment
Surveillance for those with HRC Syndromes

- **HPRC** – Hereditary Papillary Renal Cell Carcinoma (RCC)
  - Annually:
    - Physical Exam
    - Abdominal CT/MRI as surveillance for renal masses given that US can miss these lesions

Choyke et al. *J Comput Assist Tomogr* 1997
Surveillance for those with HRC Syndromes

- **BHD – Birt-Hogg-Dubé**
  - Annually:
    - Physical Exam
    - Dermatology
    - Pulmonary
  - Baseline Chest/Abdomen/Pelvis CT
    - No renal lesions – Abdominal MRI/CT every 3 years
    - Renal lesion(s) present – Annual MRI/CT

Menko et al. *Lancet Oncol* 2009
Stamatakis et al. *Fam Cancer* 2013
Surveillance for those with HRC Syndromes

• HLRCC – Hereditary Leiomyomatosis and RCC
  • Annually:
    • Physical exam
      • Dermatology
      • Gynecology
    • Abdominal MRI/CT
  • If Renal lesion(s) present – FDG/PET for staging
    • Early, aggressive surgery if renal lesion of any size detected
Surveillance for those with HRC Syndromes

• **SDH-RCC** – Succinate Dehydrogenase kidney cancer
  • Annually:
    • Physical exam
    • Abdominal MRI/CT
    • Plasma Free Metanephrines
  • If Renal lesion(s) present – FDG/PET for staging
    • Early, aggressive surgery if renal lesion of any size detected
    • Wide excision via Partial Nephrectomy if possible

Surveillance for those with HRC Syndromes

- **TSC – Tuberous Sclerosis Complex**
  - Annual Physical exam
    - Neurology
    - Dermatology
    - Dental
    - Ophthalmology
  - Brain MRI every 1-3 years (If lesion found – every year)
  - Chest CT every 5-10 years (If LAM found – every 2-3 years)
  - Cardiac Echo every 2-3 years
  - Renal Ultrasound Annually or MRI Abdomen every 1-3 years

Tuberous Sclerosis Complex Surveillance and Management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference
Surveillance for those with HRC Syndromes

• **Cowden syndrome**
  • Annually:
    • Physical exam
    • Dermatology
    • Breast – monthly self-exams
    • Thyroid
    • Gynecology
    • Labs: Fecal Occult Blood Test and Urinalysis
    • Thyroid Ultrasound
    • Transvaginal Ultrasound
    • Mammography and Breast MRI for women >30 years old
  • Every other year:
    • Abdominal US or MRI
    • Colonoscopy at age >40 years old

Shuch et al. *J Urol* 2013
Conclusions

• Hereditary Kidney Cancer may be more common than appreciated.
  • Represents more than just VHL

• A thorough exam, personal medical, and family history are invaluable.

• Genetic testing indicated in those patients 46 years-old and younger.

• Surveillance plans vary between the different syndromes.

• Multi-disciplinary collaboration is likely needed.
Conclusions

• Thank you!
• Questions?
• Comments?