Array-Comparative Genomic Hybridization (a-CGH)-Based Algorithm for Renal Tumor Subtyping in Needle Biopsies

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OBJECTIVE
- To develop a molecular assay to augment biopsy histology in subtyping renal cortical neoplasms.

INTRODUCTION
- Image-guided, percutaneous biopsy of kidney tumors is increasingly utilized, particularly in patients at higher risk of adverse outcomes.
- Biopsy results may facilitate decision-making in the management of small renal masses.
- Despite improved biopsy techniques, low yield and disrupted tissue architecture may make histologic diagnosis impossible.
- Specific genetic alterations have been identified in kidney tumors;1-3
- Accurate detection of genetic alterations may improve the diagnostic capabilities of percutaneous kidney biopsy;4
- Selected patients may avoid extirpative treatment if benign or indolent tumors are determined by biopsy.

MATERIALS
- Specimen acquisition:
  - Percutaneous 18-22 Gauge core biopsies (n = 49) from 47 renal masses and 1 enlarged LN prospectively collected from 44 patients (11/2011 – 1/2014).
- Excluded cases:
  - Cystic fluid only (1 patient);
  - No extracted DNA (1 patient).
- Techniques:
  - 1-4 core biopsies/tumor (median: 2);
  - 1-2 cores: DNA extraction for a-CGH.

Histologic Analysis:
- Diagnosis from pathology reports of biopsy tissue;
- Surgical pathology assessment used when available.

METHODS & RESULTS

Study Patient Characteristics:
- 27 Men, 19 Women
- Median Age (years): 72 (IQR: 63, 74)
- Median Tumor Size (cm): 2.7 (IQR: 1.9, 4.1)
- Median DNA extraction (µg): 2.28 (IQR: 0.88, 4.82)

Array-CGH:
- DNA extraction yielded >500 ng after QC (n = 49).
- Reference DNA: Sex-matched DNA (Promega).
- Digested and labeled DNA hybridized to targeted oligonucleotide microarrays and analyzed according to manufacturer (Agilent Technologies).
- Identification of genomic aberrations:
  - Nexus Copy Number Analysis 7.5 (BioDiscovery Inc.);
  - Histologic classification:
    - a-CGH decision tree (developed using publicly available data).
- Copy number aberrations not related to four studied renal cortical neoplasms identified as Not-Classifiable.
- Biopsies exhibiting no aberrations (other than normal variants) classified as Benign.

Array-CGH Cases:
- Total of 47 biopsies from 44 patients.
- Median maximum core size (cm): 0.7 (IQR: 0.5, 1.6)
- Pathologic Classification (n = 47): Clear cell RCC (ccRCC) = 15
  - Papillary RCC (pRCC) = 11
  - Chromophobe RCC (chrRCC) = 2
  - Unclassified RCC = 3
  - Poorly differentiated favor RCC = 1
  - Low-grade oncocyotinic neoplasm = 4
  - Low-grade smooth muscle neoplasm = 1
  - Benign/Fibrous = 3
  - Angiomyolipoma + 2
  - Oncocytoma + 2
  - High-grade urothelial carcinoma (UC) = 1
  - Non-diagnostic = 2
- Excluded cases = 2

CONCLUSIONS
- DNA yields ≤5.86 µg impaired often aCGH diagnostic capabilities.
- Overall concordance between aCGH and histology of kidney biopsy or surgical specimen was 69%.
- However, the concordance between the aCGH subtyping and surgical specimen histology was 90%.
- Other interesting observations:
  - aCGH was able to offer a definitive diagnosis (confirmed by histologic examination) of all the specimens for 2 specimens (patients 8 and 9) that were called unclassified RCC by biopsy histology.
  - Considering the overlapping morphologic features between chrRCC and UC and the difficult discrimination between these two entities based on histology alone, histology called a specimen (patient 827) as UC while molecular classification by aCGH for the same specimen was chrRCC.
  - The clinical behavior of oncocytomas, which usually present quasi genotypic changes, and low-grade oncocyotinic neoplasms, which are poorly understood, is benign. However, low-grade oncocytoinic neoplasms have the potential to be mixed with smaller components of more aggressive neoplasms. aCGH identified aberrations related to a malignant subtype in one of the four low-oncocyotinic neoplasms in this study.
- Genomic-based platforms have the potential to play a significant role in augmenting histopathology findings from core biopsy.

REFERENCES

CONFIDENCES OF INTEREST
- B.G., C.M. and J.H. are full time employees of Cancer Genetics, Inc.