Development of an Array-Comparative Genomic Hybridization (aCGH)-Based Algorithm to Assist Renal Tumor Subtyping in Needle Biopsies and Resected Specimens

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OBJECTIVE

To develop an algorithm that can accurately classify major renal cortical neoplasms based on copy number alterations (CNA) detected in biopsy DNA by aCGH.

INTRODUCTION

Image-guided, percutaneous biopsy of kidney tumors is increasingly utilized in the initial diagnosis, 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 of biopsy samples challenging.

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.

Selected patients may avoid extirpative treatment if benign or indolent tumors are determined by biopsy.

MATERIALS

Specimen acquisition:

Percutaneous 18-22 Gauge core biopsies from 44 renal masses prospectively collected from 40 patients (9/2011 - 5/2013)

Excluded 5 cases:

Clinical data (1 patient); Cystic fluid only (1 patient); insufficient material (1 patient)

Technique:

1/4 core biopsies/tumor (median: 2)

2/3 cores: DNA extraction for aCGH

Patient Characteristics:

Men: Women = 1:0.6

Histologic Analysis:

Diagnosis from pathology reports of biopsy tissue

Surplus pathology assessment used when available

METHODS AND RESULTS

Build an algorithm based on the following:

aCGH data from TCGA (analyzed using Nexus 7.0 algorithm)

489 clear cell RCC (ccRCC)

75 papillary RCC (pRCC)

65 chromophobe RCC (chrRCC)

Clear Cell (n=489)

Papillary (n=75)

Chromophobe (n=65)

In house FISH study:

127 renal cortical neoplasms needle biopsies (ex vivo)

Literature Search:

KidneyPath™

A decisive-5e algorithm based on 16 genomic aberrations

RESULTS

Array-aCGH Analysis:

DNA extraction resulted in yields >200ng after QC

Reference DNA: Sex-matched normal DNA (Promega)

Digested and labeled DNA hybridized to either targeted oligonucleotide microarray (GenaStar™) (biopsies) or whole genome 244k array (resected specimens) and analyzed according to manufacturer’s norms (Agilent)

Identification of genomic aberrations:

Nexus Copy Number Analysis 6.1 (BioDiscovery Inc.) at least 8 consecutive probes with a median log ratio greater than 0.15 or less than -0.15

Array-aCGH findings:

39 biopsies

36 biopsies: analyzable by aCGH

3 biopsies: non-diagnostic (ND) by aCGH

Low DNA yield or Poor array quality

36 diagnostic bioposes

6 biopsies classified as Benign

8 biopsies classified as ccRCC

13 biopsies classified as pRCC

3 biopsies classified as chrRCC

1 biopsy classified as OC

6 biopsies Not-classifiable

REFERENCES


CONCLUSIONS

Kidney biopsy can yield sufficient material for aCGH studies.

In this initial experience, the aCGH algorithm provided a robust and interpretable assay for tumor subclassing. Larger experience with these novel diagnostic tools is needed to determine their utility for the genomic classification of kidney tumors from kidney needle biopsies.

Reflex to FISH analysis for CCND1 rearrangement (associated with oncocytoma) should be considered for specimens that are benign by aCGH.

Mutation analysis of the VHL, or PBRM1 genes can be combined to increase the accuracy in the future.

CONFICTS OF INTEREST

C.N. is on the board of directors of Cognate Diagnostics, Inc.

INTELLECTUAL PROPERTY

C.P. Patent US 7,120,422: Panel for the Identification and Differentiation of Renal Neoplasms

RESOURCES


