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Identification of prognostic genomic markers in patients with localized clear cell renal cell carcinoma (ccRCC).

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Background: Tumor gene expression may impact prognosis following surgery for early stage ccRCC. Genomic analysis may also aid in understanding disease biology.

Methods: Patients with stage I-III ccRCC who underwent nephrectomy at CCF between 1985 and 2003 with archived paraffin-embedded nephrectomy samples were identified. Pathology and RCC recurrence status were re-reviewed and verified. Exclusions included inherited RCC, neo/adjuvant systemic therapy or <6 months follow-up. RNA was extracted from 6 x 10 μ m dissected tumor sections and RNA expression quantified for 732 genes (including 5 reference) using RT-PCR. The primary endpoint was recurrence-free interval (RFI), defined as time from nephrectomy to first recurrence or death due to RCC. The study had 80% power ($\alpha=0.05$) to identify genes associated with RFI (standardized hazard ratios (HR) ≥ 1.3).

Results: 931 patients with complete clinical/pathology data and tissue blocks were evaluable. Patient characteristics: 63% male, median age 61, stage I (68%), II (10%) and III (22%), median follow-up of 5.6 yrs. Clinical/pathology covariates significantly associated with RFI included microscopic necrosis, Fuhrman grade, stage, tumor size and lymph node involvement (all $p<0.001$). 448 genes were significantly ($p<0.05$, unadj.; Cox models) associated with RFI and 300 genes were significantly ($p<0.05$, unadj.) associated with ≥ 4 of 5 covariates. In a multivariate model, 16 genes remained significantly and strongly associated with RFI after clinical/pathologic covariate and false discovery adjustments (HR 0.68-0.80). Among the 16 genes, increased expression was associated with lower risk of recurrence for angiogenesis-related (including EMCN and NOS3) and immune-related (including CCL5 and CXCL9) genes.

Conclusions: This is the largest genomic study of localized ccRCC performed to date. Genomic factors strongly associated with risk of recurrence and clinical/pathologic covariates were identified. The magnitude of HRs are comparable to those of other clinically used prognostic markers, such as ER and HER2 in breast cancer. These results can be used to create a multi-gene algorithm to predict recurrence of ccRCC.