

[829] A 16 Gene Signature for Assessing Risk of Recurrence in Renal Cancer: Performance Beyond Conventional Pathologic Factors and Impact of Tumor Heterogeneity

Michael J Bonham, Serge Koscielny, Margarita Lopatin, Christer Svedman, Virginie Verkarre, Camelia Radulescu, Yann Neuzillet, Isabelle Hemmerle, Timsit Marc Olivier, Jean Francois Martini, James A Williams, Athanasios C Tsiatis, Dejan Knezevic, Thierry Lebret, Audrey Goddard, Arnaud Mejean, Bernard Escudier. GHI, Redwood City, CA; IGR, Villejuif, France; Necker, Paris, France; Foch, Suresnes, France; Pfizer, San Diego, CA

Background: The 16-gene Recurrence Score (RS) was developed in a cohort of 931 stage I-III ccRCC patients (pts) from Cleveland Clinic. A large prospectively-designed clinical validation study of the RS in stage I-III ccRCC pts from 1995 to 2007 at the French consortium was recently reported. The present analysis assesses the performance of the (RS) against conventional pathologic factors and tumor heterogeneity.

Design: The genes, algorithm, endpoints, methods, and analysis plan were pre-specified prior to merging clinical and molecular data. RT-PCR in fixed paraffin-embedded tissue was performed without knowledge of clinical data. Recurrence-free interval was analyzed using Cox regression stratified by stage with data censored at 5 years, and using Kaplan-Meier methods. To assess the impact of tumor heterogeneity, consistency of expression for the 16 genes and the RS was examined in a separate cohort of 8 patients with two blocks per patient and 3 different depth levels per block.

Results: RS was successfully generated in 626/645 pts (97%): 398 stage I, 54 stage II, 174 stage III. Most (71%) patients were male, 29% were ≥ 70 years, and 36% had a partial nephrectomy, 46% with tumors ≤ 4 cm, 65% with Fuhrman grade (FG) 3-4, and 27% with invasion. The continuous RS predicted recurrence risk (HR per 25 point increase in RS =3.9, 95% CI 2.6-5.8, $p < 0.001$). RS continued to predict recurrence after adjustment for tumor size, FG, and Leibovich score ($p < 0.001$). RS identified 39% of stage I pts with an average 5-yr recurrence risk of 2% (95% CI 0-7%) and 15% of pts with a 23% (95% CI 13-39%) risk. In stages II-III, RS identified 19% of pts with a 2% (95% CI 0-16%) and 44% of pts with a 39% (95% CI 29-50%) recurrence risk. The performance of RS was similar across age groups (< 60 , 60-70 or ≥ 70), gender, partial/radical nephrectomy, tumor size (≤ 4 , 4-7 or > 7 cm), FG, and presence/absence of invasion (all interaction $p > 0.29$). There was no substantial heterogeneity in single gene expression or RS (< 1 SD) both within and between blocks in the separate 8-patient study.

Conclusions: The RS is validated as a predictor of clinical outcome in stage I-III ccRCC patients providing significant information beyond conventional pathologic measures. Gene expression variability within and between blocks for the 16 gene RS was low, indicating that the assay has a robust performance despite tumor heterogeneity.

Category: Genitourinary Pathology (including Renal tumors)

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