Aim: New clinical tools are needed to improve risk assessment in ccRCC. The 16-gene (11 cancer related, 5 reference) 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 diagnosed from 1995 to 2007 at the French consortium was recently reported. The present analysis assesses the performance of the score in clinically relevant subgroups.

Methods: The genes, algorithm, endpoints, methods, and analysis plan were pre-specified prior to merging clinical and molecular data. RT-PCR in fixed paraffin-embedded primary ccRCC 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 Kaplan-Meier methods.

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 or older, 36% with partial nephrectomy, 46% with tumors ≤4 cm, 65% with Fuhrman grade 3-4, and 27% with invasion. Median follow-up was 5.5 yrs. The continuous RS predicted recurrence risk (HR per 25 point increase in RS (HR/25) =3.9, 95% CI 2.6-5.8, p < 0.001). RS continued to predict recurrence after adjustment for tumor size and Fuhrman grade (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 the age groups (<60, 60-70 or ≥70), gender, partial or radical nephrectomy, tumor size (≤4, 4-7 or >7 cm), Fuhrman grade, and presence/absence of invasion (all interaction p > 0.29).

Conclusions: The 16-gene RS is validated as a predictor of clinical outcome in pts with stage I-III ccRCC and provides significant information beyond conventional pathologic measures. The performance of the score was similar across a wide range of clinically relevant covariates indicating potential broad utility.

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