

Robustness of the 16-gene signature for prediction of recurrence-free interval in localized clear cell renal cell carcinoma.

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Background: The Renal Cancer assay is a clinically validated RT-PCR assay developed to estimate the risk of recurrence in stage I-III clear cell renal cell carcinoma (ccRCC) patients (pts) treated with nephrectomy. The assay measures expression of 16 genes that are combined to calculate the Recurrence Score result (RS). The RS is associated with recurrence, renal cancer-specific survival and overall survival (all $p < 0.001$) (Escudier, ASCO 2014). The performance of the RS in clinically relevant subgroups, compared to the Leibovich score, and its within-patient variability was examined. Methods: The algorithm, endpoints, methods, and analysis plan were pre-specified prior to merging clinical and molecular data. RT-PCR of RNA from fixed paraffin-embedded ccRCC tissue was performed without knowledge of clinical data. Recurrence-free interval (RFI) was analyzed using Cox regression stratified by stage with data censored at 5 years, and Kaplan-Meier methods. Multivariable models incorporating the Leibovich score were used to assess the additional contribution of the RS to prediction of recurrence. Within- and between-tumor block reproducibility was assessed in an independent study using two separate tumor blocks from 8 pts, where each block was analyzed at 3 depths. Results: RS was generated in 626/645 pts (97%): 398 stage I, 54 stage II, 174 stage III. Median follow up was 5.5 yrs. The RS was significantly associated with risk of recurrence after adjustment for the Leibovich score (HR=4.20, $p < 0.001$). Additionally, the performance of RS was similar across age groups (<60, 60-70 or ≥ 70), gender, nephrectomy type, tumor size (≤ 4 , 4-7 or > 7 cm), grade, and presence/absence of invasion (all interaction $p > 0.29$). Within-patient variability in the score (std. dev. of 1.73 and 4.74 RS units for within- and between-tumor block, respectively) was lower than patient-to-patient variability (std. dev. of 15.6 in validation study). Conclusions: The 16-gene signature remains strongly associated with risk of recurrence after adjustment for the Leibovich score and performs consistently across clinically relevant subgroups. Examination of within-patient and between-patient variability indicates that the score is robust to tumor heterogeneity.