61

Leveraging a robust patient-derived xenograft platform to characterize predictors for engraftment and oncologic outcomes in renal cell carcinoma patients

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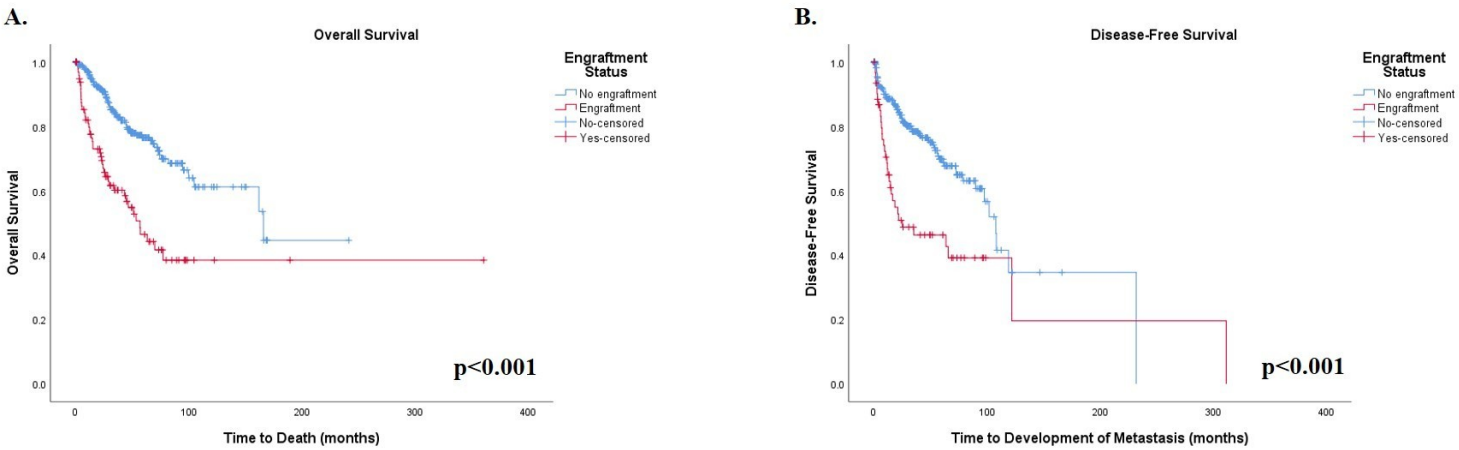
Introduction & Objectives: Patient-derived xenograft (PDX) models of renal cell carcinoma (RCC) preserve the biological features of patient tumors, providing a platform for biomarker identification and preclinical drug testing. We sought to identify predictors of successful tumor engraftment and evaluate the prognostic value of engraftment in patients with RCC using a robust murine PDX platform.

Materials & Methods: 1,200 specimens derived from nephrectomy, thrombectomy, metastasectomy, or biopsy were orthotopically (renally) implanted into NOD/SCID mice between 2008-2018. Non-RCC pathology was excluded. Stable engraftment was defined by successful passage of tumor tissue at least twice with histologic confirmation. Clinicopathologic characteristics were stratified by engraftment status, and multivariate (MVA) logistic regression was used to identify predictors of engraftment. Kaplan-Meier and Cox regression analyses were used to assess the prognostic value of engraftment on patient overall (OS) and disease-free (DFS) survival.

Results: 1,003 independent PDX lines derived from 770 RCC patients were included. 157 (15.6%) lines successfully engrafted and exhibited higher tumor grade, stage, size, and presence of sarcomatoid or rhabdoid components. Whole exome sequencing was performed on 230 PDX lines. On MVA, sarcomatoid (OR 5.71, $p<0.001$), rhabdoid (OR 2.79, $p=0.046$), and advanced stage (OR 1.72, $p=0.049$) were significant predictors for engraftment, while high grade and metastatic tumor source were significant only on UVA. Engraftment was associated with poor OS (HR 2.11, $p<0.001$) and DFS (HR 1.85, $p=0.020$) in patients after controlling for sarcomatoid, rhabdoid, grade, stage, and age on MVA and reflected in Kaplan-Meier analysis (Figure).

Figure. Kaplan-Meier curves for (A) OS and (B) DFS in humans, stratified by successful stable engraftment in mice. Engraftment was significantly associated with worse OS ($p<0.001$) and DFS ($p<0.001$).



Conclusions: Aggressive RCC biology correlates with successful engraftment in PDX models. Engraftment remains independently predictive of OS and DFS even after controlling for adverse pathologic features. Engraftment in mice may illuminate aspects of tumor biology not captured by clinicopathologic variables and provide insight into novel determinants of tumor aggressiveness and metastasis. Efforts are underway to elucidate genomic drivers of engraftment.