70 Genomic categorization of high-grade unclassified renal cell carcinoma to refine prognostication and therapeutic approach

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Introduction & Objectives: Unclassified renal cell carcinoma (uRCC) makes up a large portion of aggressive non-clear cell RCC that shows limited response to standard therapeutic regimens. At present, clinical and pathologic parameters or biomarkers to stratify this heterogeneous group of tumors are missing. We recently reported a molecular analysis of 62 high-grade primary uRCC [“discovery cohort (DC)”] and identified distinct molecular subsets. We aim to validate this molecular stratification in an independent clinical cohort and further investigate the clinicopathologic and molecular features that help improve prognostication and direct management.

Materials & Methods: The diagnosis of uRCC, based on current WHO criteria, was established at our institution by experienced genitourinary pathologists. Tumor specimens from 75 patients (validation cohort) with uRCC were profiled using our institutional panel (MSK-IMPACT®). Germline testing results were available in 37 cases. Allele-specific copy number analysis was used to characterize putative driver copy-number alterations. Clonality estimates, computed using allelic frequencies, and purity/ploidy estimates were used to further refine the genomic groupings. Survival analysis was performed using the Kaplan-Meier method and Cox regression model.

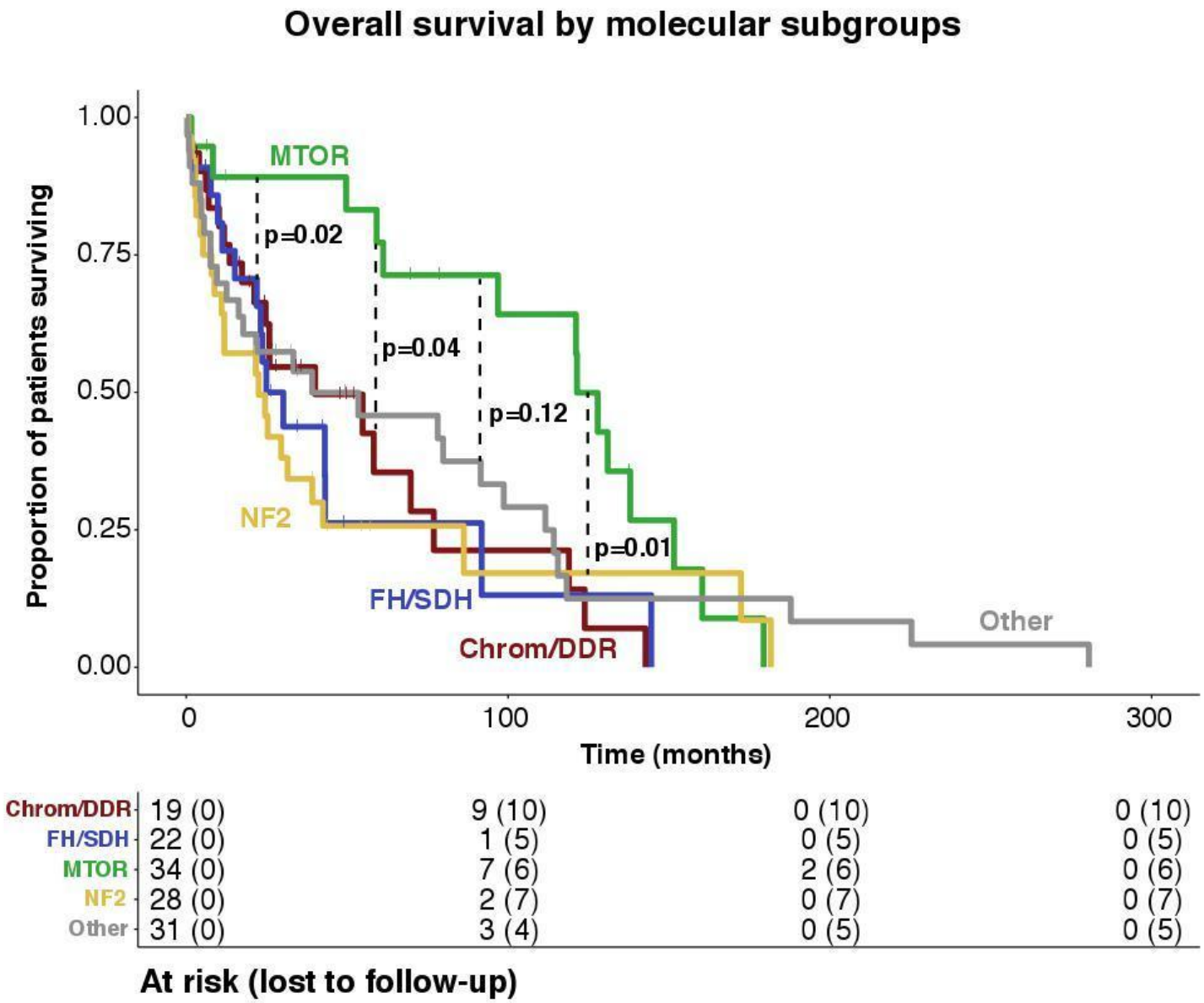
Results: The frequency of somatic mutations in the validation cohort was highly consistent with findings in the DC. Germline alterations were detected in previously unsuspected cases. The integrative analysis supported the presence of five major molecular subsets. The molecular subgroups and results of the survival analysis are provided in Tab.1 and Fig.1. Univariate Cox regression analysis showed a significantly worse outcome associated with the *NF2-loss* group. Clonality analysis confirmed the previously described putative drivers as early oncogenic events. Further, we identified rare cases with alterations indicating sensitivity or resistance to immunotherapy.

Tab.1: Molecular subgroups and results of survival analysis:

Molecular subgroup	VC (n)	Combined DC + VC (n)	HR (95% CI)	p value
MTOR	8	21	1	
NF2	14	29	2.56 (1.30 - 5.06)	0.01
Chrom/DDR	18	31	2.07 (1.04 - 4.15)	0.04

FH/SDH	18	22	2.37 (1.12 - 5.01)	0.02
Other	17	34	1.69 (0.87 - 3.28)	0.12

Fig.1:



Conclusions: Molecular stratification of high-grade uRCC aides to improve prognostication and provides rationale for different therapeutic strategies.