O4 Molecular subtypes of fully resected clear cell renal cell carcinoma are prognostic for risk of relapse and may impact adjuvant treatment

European Urology Open Science 2020;21(Suppl 3):S91

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Introduction & Objectives: Most trials with adjuvant vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) have failed to demonstrate significant benefit in high-risk fully resected clear-cell renal cell carcinoma (ccRCC). Leibovich score is widely used as a predictive tool for risk of relapse and a selection criterium in adjuvant trials, but categories remain heterogeneous. Previously described molecular subtypes ccrcc1 to ccrcc4 as well as angiogenic gene signature are predictive for response to VEGFR-TKIs in metastatic ccRCC (m-ccRCC). We hypothesized that molecular subtypes could be an adjunct to improve the characterization of tumors at high risk of relapse and select patients for adjuvant treatment.

Materials & Methods: Patients with metachronous m-ccRCC were included. We tested the associations between Leibovich score, molecular classification and angiogenic as well as immunogenic gene signatures. Logistic regression, Kaplan-Meier survival analysis and Cox proportional hazards regression models were used to test associations, time to metastasis (TTM) and significant predictors.

Results: Seventy-five patients were included: 5 were Leibovich low, 24 intermediate and 43 high risk. The unfavorable ccrcc1&4 subtypes had significantly higher Leibovich scores compared to the favorable ccrcc2&3 (p=0.006), whereas the favorable ccrcc2&3 subtypes had higher angiogenic gene signatures (p=0.0002). Leibovich risk category, however, was not significantly associated with TTM (HR 1.51, 95%CI 0,90-2,52, p=0.12). Contrarily the molecular subtypes were prognostic for TTM, with median TTM 42 vs 14 months for the favorable vs unfavorable risk molecular subtypes (HR1.70, 95%CI 1,01-2,85, p=0.046). High angiogenic gene signature was also associated with longer TTM (median 41 vs 17 months, HR 2.41, 95%CI 1,51-3,86, p=0.016). Immunogenic gene signatures were not associated with TTM (p=0.64) and not associated with Leibovich score (p=0.79). High immunogenic gene signatures were mostly found in the unfavorable ccrcc4 subgroup, and the favorable ccrcc2 subgroup.

Conclusions: Molecular subtypes can further refine prognostic information with regards to risk of relapse in fully resected ccRCC, especially in the heterogeneous Leibovich intermediate and high risk subgroups. Favorable ccrcc2&3 tumors with high angiogenic signature, who respond best to VEGFR-TKIs, are at lower risk of relapse. This could at least partially explain why most adjuvant trials with VEGFR-TKIs in high risk fully resected ccRCC have failed to demonstrate significant benefit. Trials with (neo-)adjuvant immune checkpoint inhibitors are ongoing, but since Leibovich score is not correlated with immunogenic gene signature it might not help to select patients who will benefit. The molecular characterization, however, could serve as a biomarker to guide adjuvant treatment for patients at high risk of relapse.