Association of machine learning (ML)–derived histological features with transcriptomic molecular subtypes in advanced renal cell carcinoma (RCC)

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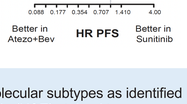
BACKGROUND

- Metastatic RCC (mRCC) is a molecularly heterogeneous disease with varying levels of angiogenic presence, immune infiltration, and PD-L1 expression[1,2]
- Transcriptomic analysis in the Phase 3 IMmotion151 trial identified 7 molecular subtypes that showed differential outcomes to atezolizumab + bevacizumab vs sunitinib treatment[2]

Figure 1. Forest plots for PFS hazard ratios in patients treated with atezolizumab + bevacizumab (A/B) versus sunitinib by transcriptomic clusters.[1]

Cluster	PFS HR (95% CI)	p-value	A/B mPFS	Sunitinib mPFS
1 - Angio/stromal	1.11 (0.65−1.88)	0.708	15.3	13.9
2 - Angiogenic	1.16 (0.82−1.63)	0.397	13.8	14.2
3 - Complement/Ω-ox.	0.92 (0.63−1.34)	0.666	8.1	7.1
4 - T-eff/Proliferative	0.52 (0.33−0.82)	0.005	10.9	6.1
5 - Proliferative	0.47 (0.27−0.82)	0.007	8.3	4.3
6 - Stromal/Proliferative	0.81 (0.52−1.25)	0.331	6.8	5.2
7 - snoRNA	0.10 (0.01−0.77)	0.028	NR	7.4



mPFS, median PFS.

- Here, we present histological correlates of these molecular subtypes as identified in whole slide images (WSI) of hematoxylin and eosin (H&E) stained tumors

Objectives

- Develop machine learning (ML) models to derive histological features in mRCC tumors[3]
- Identify histological correlates of RCC molecular subtypes on H&E WSI and evaluate them as surrogate imaging-based predictive biomarkers

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METHODS

This exploratory analysis using WSI evaluated imaging-based features and their association with molecular subtypes and clinical outcomes in untreated mRCC

- ML models identified 922 H&E derived, human interpretable histological features in RCC associated with tumor and stromal (including blood vessels, immune cells, and fibroblasts) cell and tissue morphologies, and nucleus shape
- These ML human interpretable histological features were then extracted from WSI in 2 mRCC trials: IMmotion151 (n= 97, discovery cohort) and IMmotion150 (n=203, validation cohort)
- As previously described,[2] 7 molecular subtypes were combined into 4 subgroups: Angiogenic (comprised of Angiogenic/Stromal and Angiogenic), Complement/ Omega Oxidation, T-effector, and Proliferative (comprised of Proliferative and Stromal Proliferative) for computational power. The snoRNA subset was excluded from this analysis due to prohibitively low prevalence
- Univariate analysis with false discovery rate (FDR) correction was applied to identify positively associated human interpretable features in each of the 4 subgroups in the IMmotion 151 WSIs and then validated in IMmotion150 molecular subgroups
- Representative ML human interpretable features that showed uniquely higher abundance in each molecular subgroup in both studies were dichotomized by tertiles as 'high' or 'low/intermediate' and were associated with progression free survival (PFS) to fit Cox proportional hazard models in the IMmotion151 study

Human interpretable feature extraction from H&E-stained WSI

Figure 2. ML models were deployed on H&E-stained WSI to predict A) tissue types, B) blood vessel regions, and C) cell types. Features were extracted from these models, examples of which are shown in panel C.

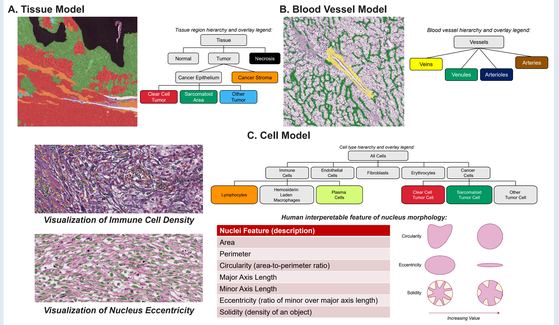


Figure 3. Heatmap showing unsupervised analysis of feature similarity using hierarchical clustering. A total of 18 clusters were constructed, which were later used for dimensionality reduction.

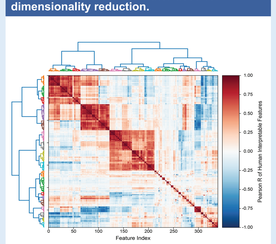
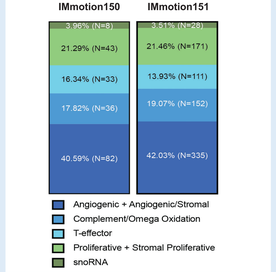


Figure 4. Distribution of molecular subtypes in the IMmotion150 and IMmotion151 cohorts.



RESULTS

Distinct imaging based phenotypes are associated with each RCC molecular subgroup

- The Angiogenic subgroup had a higher prevalence of 40 imaging-based features associated with density of endothelial cells and vessels in the cancer epithelium
- The T-effector subtype showed higher abundance of 64 imaging-based features associated with immune cell presence in stroma
- The Proliferative subgroup showed higher prevalence of 40 imaging-based features associated with nuclear morphologies
- No imaging-based features were uniquely expressed for Complement/ Omega oxidation subgroup

Representative histological correlates of RCC molecular subgroups in H&E WSI

Figure 5. Within the discovery cohort, IMmotion151, box plots (Mann-Whitney U test, with 5% FDR correction) are shown for the imaging-based human interpretable features for the (A) Angiogenic, (B) T-effector, and (C) Proliferative patient subsets in a one vs rest setting, respectively.

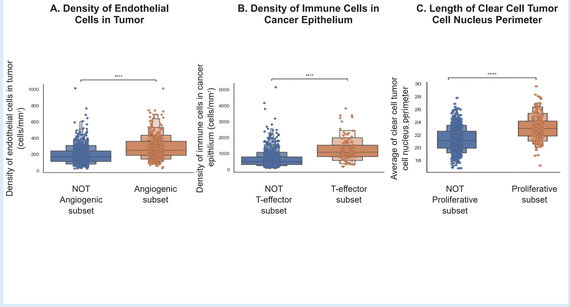
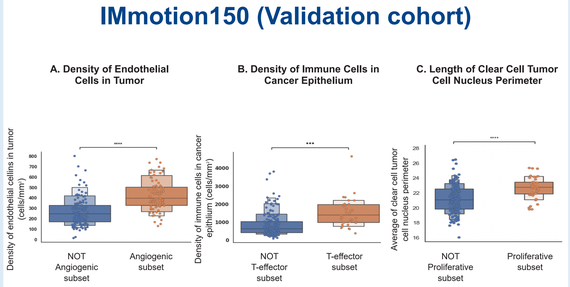
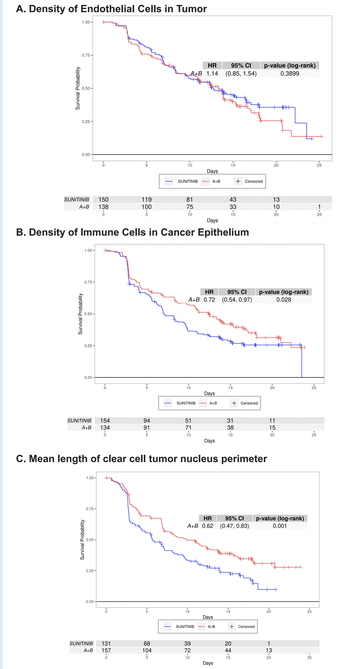


Figure 6. Within the validation cohort, IMmotion150, box plots (Mann-Whitney U test, with 5% FDR correction) are shown for the imaging-based human interpretable features for (A) Angiogenic (B) T-effector, (C) Proliferative patient subsets in a one vs rest setting respectively.



Representative human interpretable features enriched in T-effector and Proliferative subgroups showed improved PFS benefit with atezolizumab + bevacizumab compared to sunitinib

Figure 7. Association of differentially abundant human-interpretable features with PFS outcomes in IMmotion151.



(A) Higher abundance of 'Density of endothelial cells in tumor tissue" feature showed similar PFS to atezolizumab+ bevacizumab vs sunitinib.

(B) Higher abundance of "Density of lymphocytes in cancer epithelium" feature associated with improved PFS with atezolizumab+bevacizumab vs sunitinib.

(C) Higher abundance of "Mean length of clear cell tumor nucleus perimeter" feature was associated with improved PFS with atezolizumab+bevacizumab vs sunitinib.

HR, hazard ratio. A+B; atezolizumab + bevacizumab. HRs displayed for exploratory/descriptive purposes only.

CONCLUSIONS AND FUTURE DIRECTIONS

- We identified unique histological features of RCC tumors that correlate with previously defined molecular subtypes and associate with differential clinical outcomes[1]
- Our results suggest that clinically relevant RCC subtypes can be extracted directly from H&E-stained WSI and may complement gene expression based patient stratification and selection strategies
- Further prospective validation of a possible biomarker-directed approach to 1L RCC treatment is warranted

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DISCLOSURES

- Niha Beig reports Roche stock or stock options

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