



Kidney Cancer Research Summit **KCRS21**

Histologic Growth Patterns in Nephrectomy Specimens of Clear Cell Renal Cell Carcinoma Inform Tumor Evolution

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Disclosures

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No financial relationships to disclose.

Background

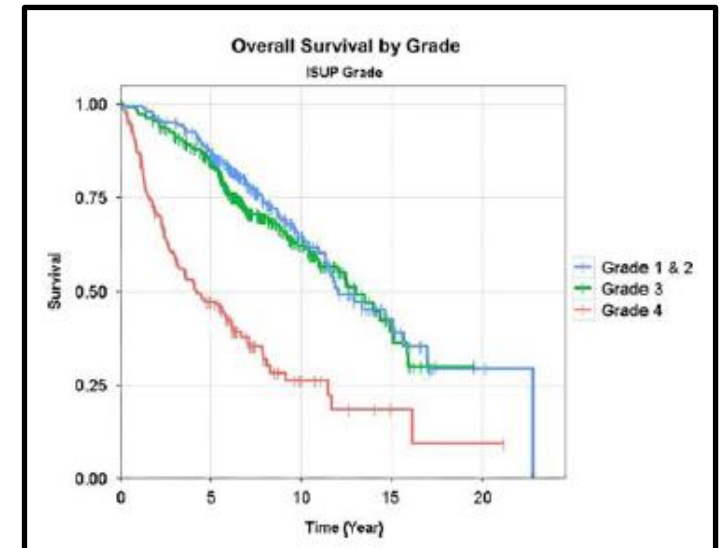
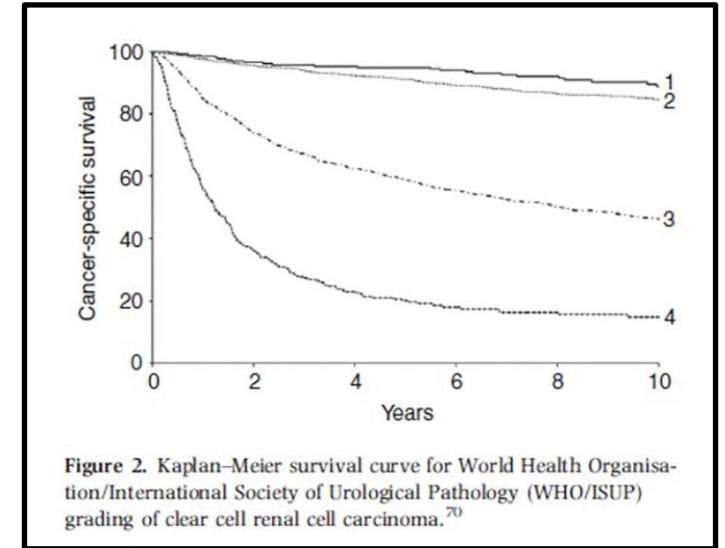
- 30% of patients with metastatic disease at presentation
- 30% of patients with localized disease develop metastasis
- Predicting the risk of metastatic progression after surgery is challenging and currently relies solely on clinical variables

Siegel RL et al. CA Cancer J Clin 2018;68:7-30.
Dabestani S et al. World J Urol 2016;34:1081-6.
Rabinovitch RA et al. J Clin Oncol 1994;12:206-12.

WHO/ISUP Grading System

Nucleolar Grade	Prevalence	Criteria
1	9%	Size of nucleoli
2, 3	64-85%	Size of nucleoli
4	7-20%	Sarcomatoid, rhabdoid, multinuclear giant cells, extreme nuclear pleomorphism

Differences in outcomes for grades 2, 3: conflicting results



Delahunt B et al. Am. J. Surg. Pathol. 2013; 37; 311–322
 Dagher J et al. Histopathology 2017;71:918-25
 Khor LY et al. Am J Surg Pathol 2016;40:1224-31

Hypothesis

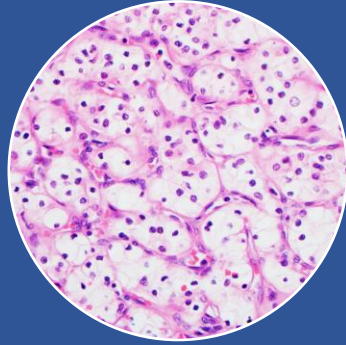
We hypothesized that progression from low-grade to high-grade in ccRCC is related to the evolution of HGPs and may define a tumor evolutionary tree.

Study Design



107 metastatic cases

40 non-metastatic with at least 3 year follow up



24 Histologic growth patterns in primary tumor



Association with overall survival (OS) adjusting for multiple variables

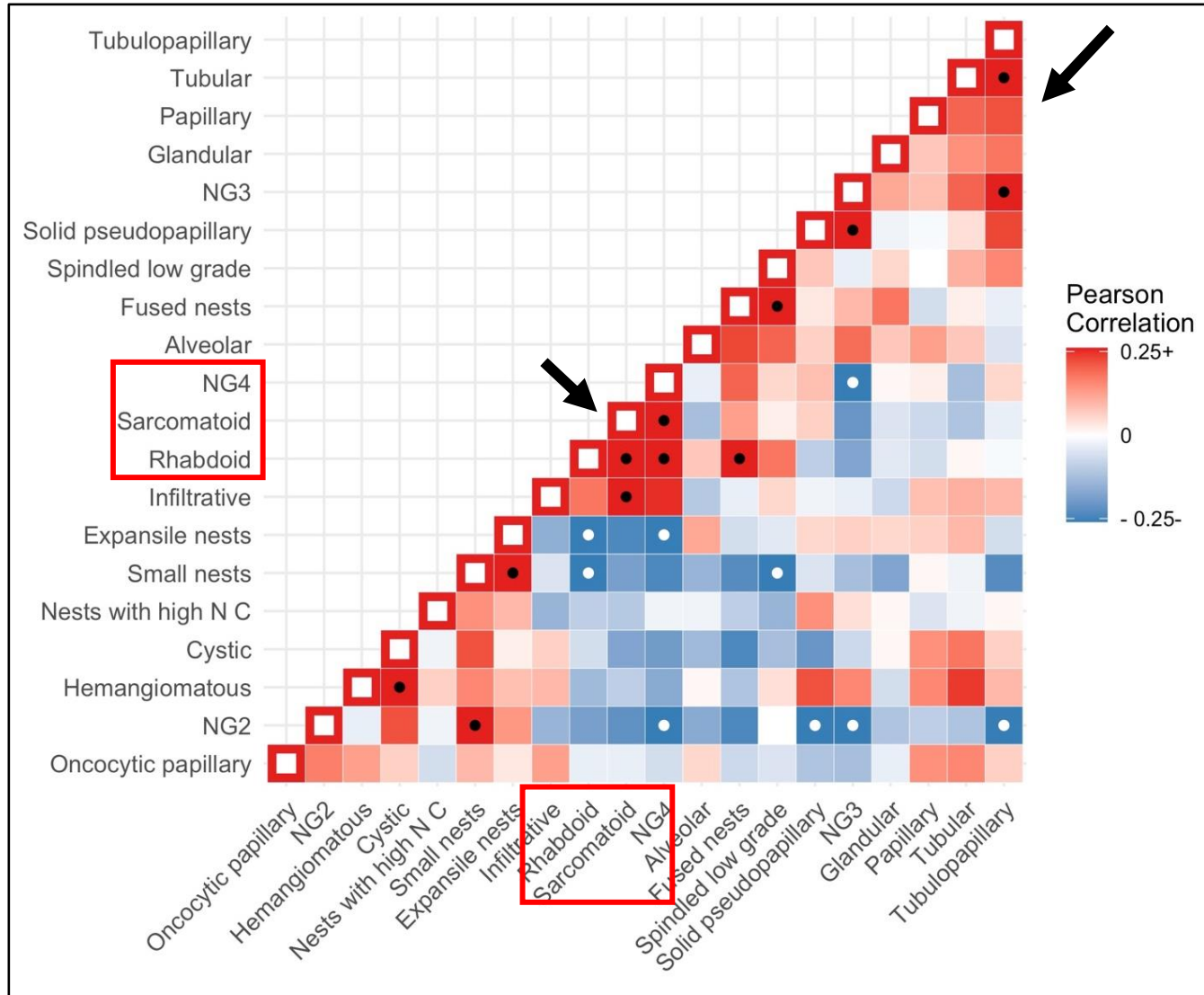


Baseline Characteristics

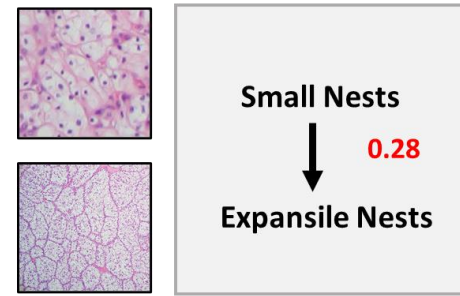
	Metastatic N = 107 (%)	Non-metastatic N = 40 (%)	P-value
Age at nephrectomy (median)	60.76	56.19	0.001
Gender = M	79 (73.8)	19 (47.5)	0.005
Tumor size (median)	9.15	3.70	< 0.001
Extra-renal extension	68 (63.6)	7 (17.5)	< 0.001
Renal vein thrombosis	46 (43.0)	4 (10.0)	0.001
pTN stage (pTNM, AJCC 8th Edition)		30	
T1aNx/N0	17	-	
T1N1	2	-	
T2Nx/N0	9	-	
T2N1	2	10	
T3Nx/N0	56	-	
T3N1	15	-	
T4	6	-	
IMDC* category		N/A	
Favorable	14 (13.1)		
Intermediate	66 (61.7)		
Poor	27 (25.2)		
Nucleolar grade			< 0.001
2	30 (28.0)	34 (85.0)	
3	54 (50.5)	6 (15.0)	
4	23 (21.5)	0 (0.0)	
Necrosis	76 (71.0)	10 (25.0)	< 0.001
Median number of HGPs (range)	5.0 (2-13)	4.0 (2-9)	0.003

■ Median Follow-Up: 6 years

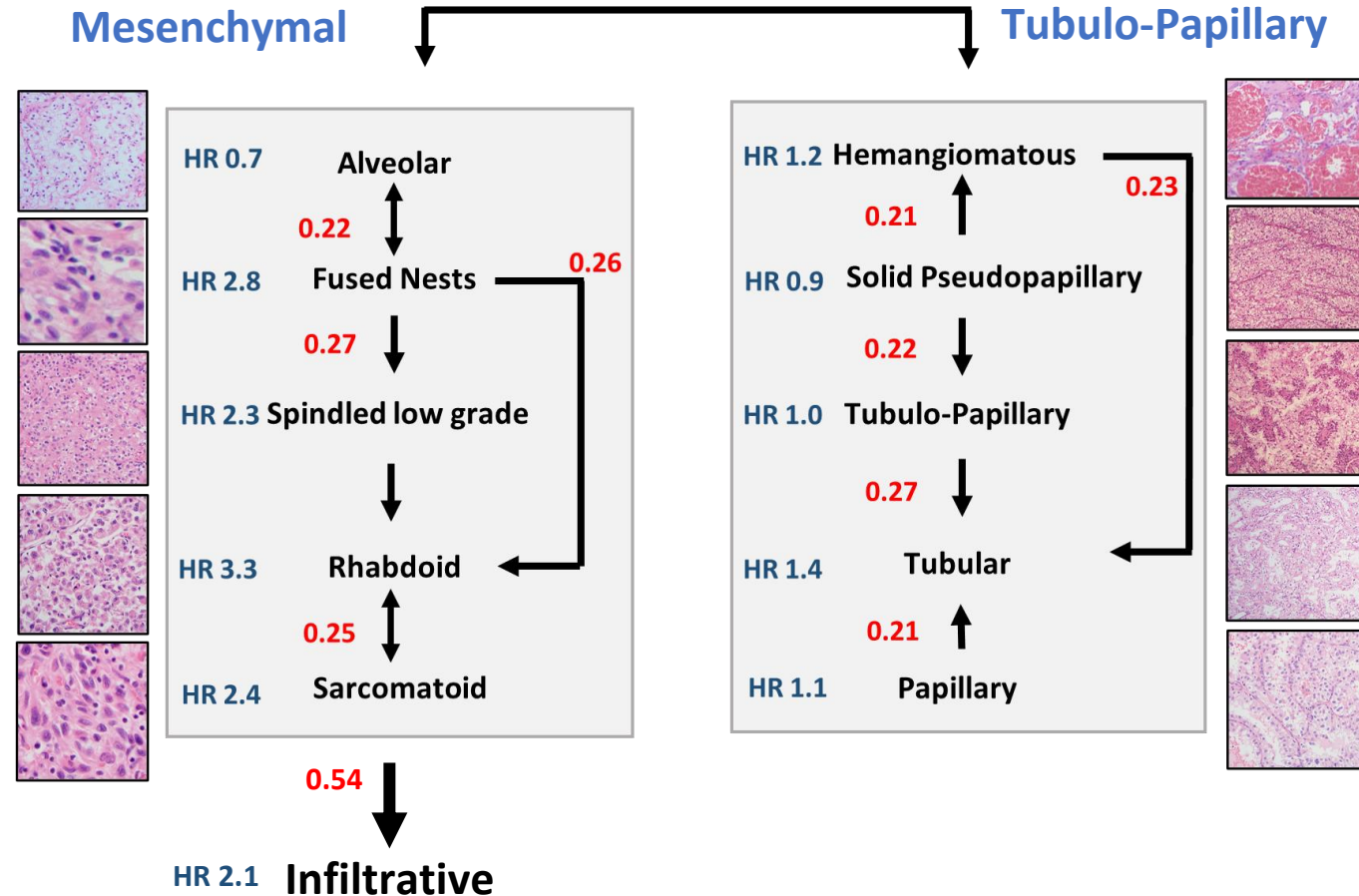
Pairwise Correlation Matrix



Tumor Evolutionary Tree



- Of 107 metastatic cases, 44 exhibited mesenchymal differentiation, while only one case with mesenchymal differentiation was detected in the non-metastatic group
- Both these pathways were mutually exclusive in majority of cases.



Conclusions

- ccRCC start as small compact nests that evolve through epithelial and mesenchymal differentiation, the latter being almost exclusively seen in cases that metastasize.
- However, the observation that significant number of metastatic cases lack mesenchymal differentiation suggest the emergence of metastatic cell clones may occur in tubulopapillary epithelial HGPs.
- Identifying molecular drivers in cancer regions of tubulopapillary morphology will be an important next step for identifying novel therapeutic targets.


Thank You!



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