Genomic Predictors of Pathological Upstaging of Clinically Localized Urothelial Carcinoma at Radical Cystectomy

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Introduction

- Neoadjuvant chemotherapy (NAC) is standard of care for clinically localized urothelial carcinoma
- Despite level 1 evidence, use of NAC remains low
- Unfortunately, upstaging of cT1-T2 urothelial carcinoma to non-organ confined pathological stage ≥T3 or N+ at radical cystectomy (RC) is common
- Biomarkers to stratify patients who have NOC disease are limited
- Prior studies, including the urothelial TCGA, have demonstrated that luminal tumors are associated with lower rates of pathological upstaging at RC
- Luminal tumors are enriched with *FGFR3* alterations, we sought to identify genomic predictors of upstaging

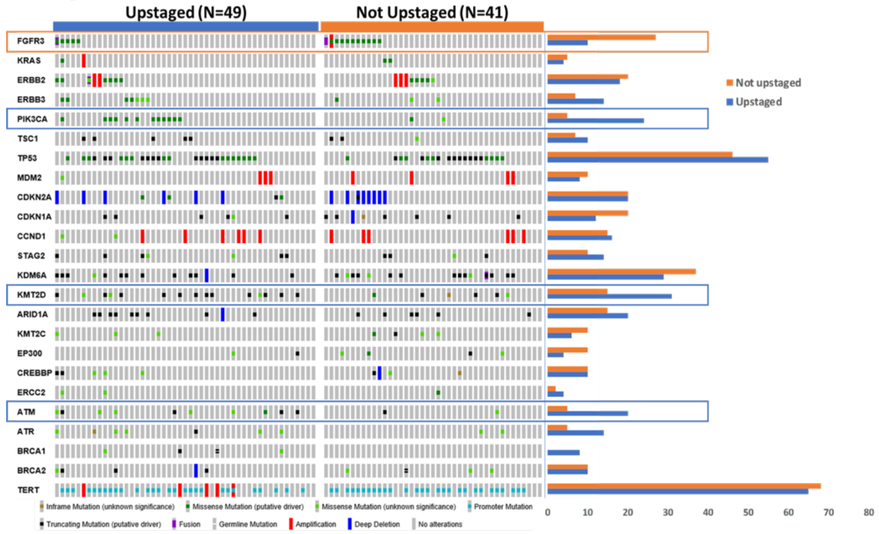
Methods

- Identified patients with high-grade, cT1-2, N0M0 urothelial carcinoma who underwent RC without NAC
- Final pathology reviewed, upstaging was defined as pT3/T4 and/or pTanyN1-3 at RC
- Targeted capture-sequencing (MSK-IMPACT) of the TUR or RC specimen was performed
- Clinical and sequencing data was compared between those upstaged and those not upstaged

Results

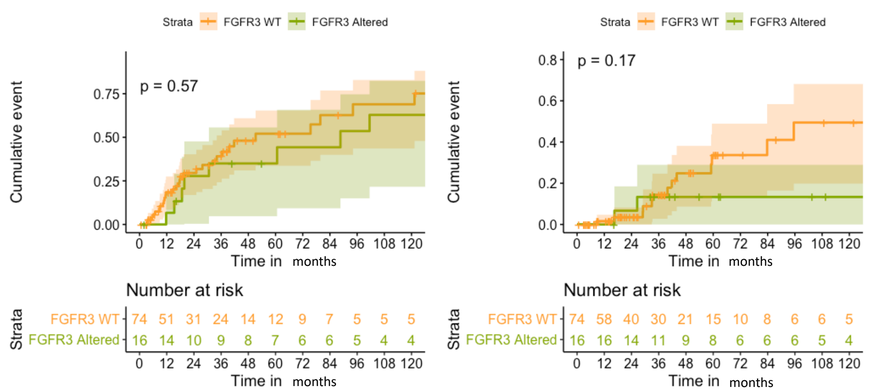
- 90 patients who met inclusion criteria, 49 (54%) were upstaged
- 35% of cT1 and 83% of cT2 were upstaged
- **Table** demonstrates no significant association of upstaging with age, gender, smoking status or prior BCG exposure

Figure



- *FGFR3* alterations were significantly associated with not upstaged tumors (27% vs 10%, 0.047)
- *PIK3CA* (3% vs 24%, p=0.008), *KMT2D* (12% vs 31%, p=0.047) and *ATM* (5% vs 20%, p=0.048) alterations were significantly associated with upstaging
- Recurrence-free survival and cancer-specific survival were not significantly different between those *FGFR3* altered and wild-type even when stratified for cT1 vs cT2

Recurrence-Free Survival Cancer-Specific Survival



Table

Characteristic[1]	Not upstaged N = 41	Upstaged N = 49	p-value[2]
Gender			0.5
M	0 (0%)	3 (25%)	
F	6 (100%)	9 (75%)	
Age (years)	66 (58, 74)	68 (60, 77)	0.29
Smoking status			0.18
Active/Former	21 (51%)	33 (67%)	
Never smoker	20 (49%)	16 (33%)	
Prior BCG Exposure	17 (41%)	12 (24%)	0.14
Clinical T1	35 (85%)	19 (39%)	**<0.001**
Adjuvant Chemo	0 (0%)	16 (33%)	**<0.001**

[1] Statistics presented: n (%); median (IQR)
[2] Statistical tests performed: Fisher's exact test; Wilcoxon rank-sum test

Conclusion

- Despite low use of NAC, there remains a majority of patients who would benefit given a high rate of upstaging
- In a select cohort of patients without NAC, we have identified multiple genomic predictors of upstaging
- It is surprising that *PIK3CA* was associated with upstaging
- As luminal tumors are often enriched with *FGFR3* alterations, it held true that these tumors were not upstaged
- We are prospectively validating these findings to provide further credence that these tumors are more likely to harbor NOC disease
- Utilization of genomic predictors should provide a biomarker to increase the utilization of NAC

This work was supported by the Sidney Kimmel Center for Prostate and Urologic Cancers, the Michael and Zena Wiener for Therapeutics Program in Bladder Cancer, Pin Down Bladder Cancer, Cycle for Survival, the Marie-Josee and Henry R. Kravis Center for Molecular Oncology, NIH/NCATS Grant Number UL1-TR002384, the National Cancer Institute Cancer Center Core Grant Number P30-CA008748 and by SPORE in Bladder Cancer P50-CA221745.