Actionable genomic landscapes from a real-world cohort of localized urothelial carcinoma patients

Abstract #: 525

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INTRODUCTION

Recent targeted therapies for advanced and metastatic urothelial cancer have generated enthusiasm, but the actionable genomic landscape of early-stage disease remains largely unknown. Here, we used real-world evidence to investigate differences between somatic and germline mutations in localized, early-stage and advanced urothelial cancers.

METHODS

We retrospectively analyzed de-identified next-generation sequencing (NGS) data from 1,146 bladder cancer patients (stages I-IV) with formalin-fixed, paraffin-embedded tumor biopsies sequenced using the Tempus xT solid tumor assay (DNA-seq of 595-648 genes at 500x coverage; whole-exome capture RNA-seq). For the subset of patients with tumor-normal match sequencing (n=758), additional incidental germline alterations in 46 different genes were assessed.

Cohort Demographics

Characteristic	Stages I-II, N = 124	Stage III, N = 159	Stage IV, N = 863
Age at Diagnosis Median (IQR)	73 (63, 79)	72 (63, 77)	68 (61, 75)
Unknown	22	38	256
Gender			
Male	96 (77%)	118 (74%)	633 (73%)
Female	28 (23%)	41 (26%)	230 (27%)
Race			
White	66 (81%)	87 (84%)	443 (89%)
Black or African American	9 (11%)	5 (4.9%)	31 (6.2%)
Asian	1 (1.2%)	6 (5.8%)	12 (2.4%)
Other Race	5 (6.2%)	5 (4.9%)	13 (2.6%)
Unknown	43	56	364
Ethnicity			
Not Hispanic or Latino	39 (95%)	37 (90%)	189 (88%)
Hispanic or Latino	2 (4.9%)	4 (9.8%)	25 (12%)
Unknown	83	118	649

Table 1. Observed differences across gender, race, and ethnicity according to stage were not significant (p>0.05, Pearson's Chi-squared test). Age distribution differed significantly across stage (p=0.006, Kruskal-Wallis rank sum test).

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RESULTS

Assessing the immunogenic landscape of bladder tumors

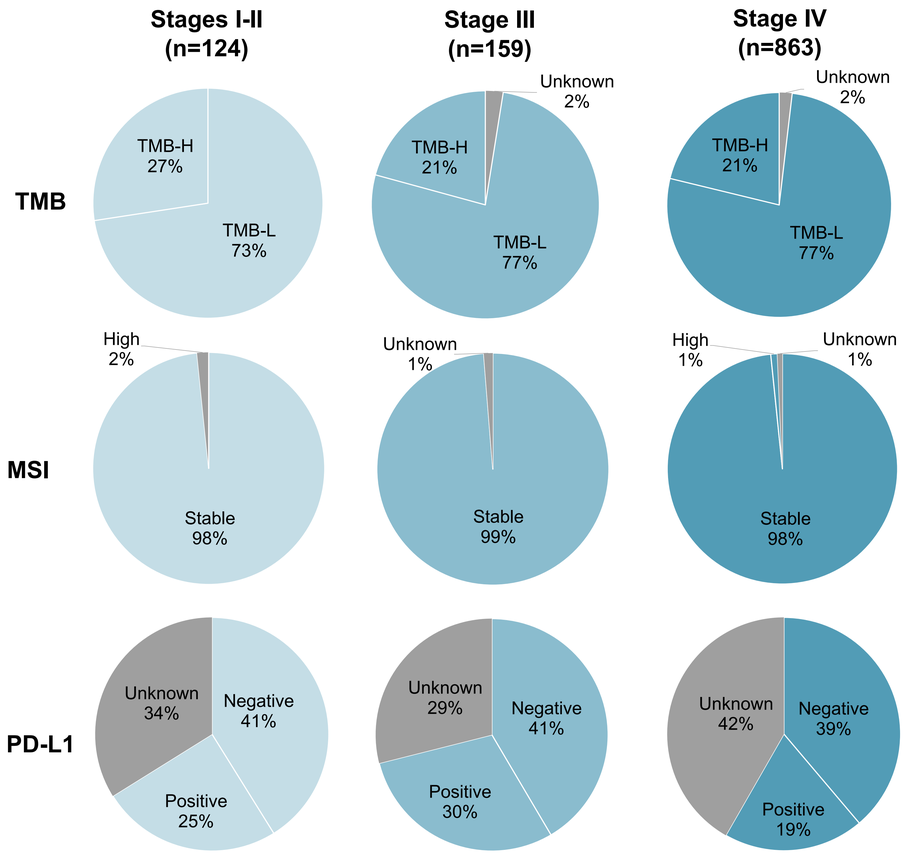

Figure 1. We analyzed tumor mutational burden (TMB), microsatellite instability status (MSI), and PD-L1 immunohistochemical staining according to stage. TMB high (TMB-H) is defined as ≥10 mutations per megabase (muts/MB), while TMB low (TMB-L) is defined as <10 muts/MB. MSI status was assessed using probes across 43 microsatellites regions. We did not observe significant differences in either TMB status, MSI status, or PD-L1 positivity according to stage (all cases, p>0.05). Note that 29-42% of patients across stages did not have PD-L1 results, which influenced the overall rate of positivity.

Investigating the prevalence of somatic variants across stages

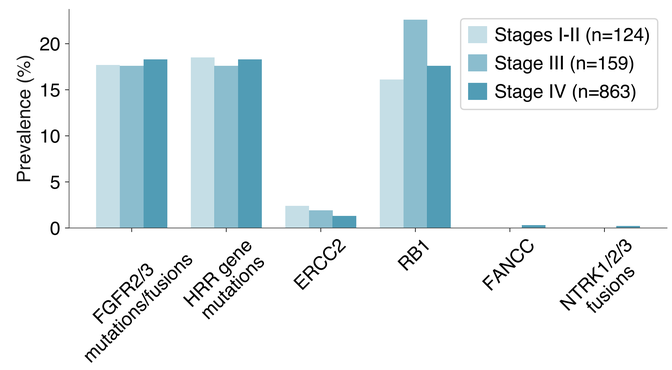

Figure 2. NGS identified single nucleotide variants, insertions/deletions, and copy number variants in *FGFR2/3*, homologous recombination repair (HRR) genes, additional DNA repair genes (*ERCC2*, *RB1* and *FANCC*), and fusions in *NTRK1/2/3* at similar frequencies across disease stages. HRR genes included *ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCA, FANCL, HDAC2, MRE11, NBN, PALB2, RAD51B, RAD51C, RAD51D,* and *RAD54L*. Significant differences were not observed in alterations in these genes according to stage (all cases, p>0.05).

Detecting germline mutations via tumor/normal matched sequencing

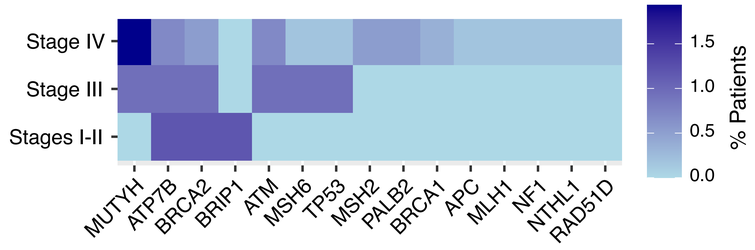

Figure 3. In a subset of 758 patients with tumor/normal matched sequencing (stages I-II: 84, III: 105, and IV: 569), we identified a low rate of incidental germline mutations in *MUTYH* (III, 1%; IV, 1.9%), *BRCA2* (I-II, 1.2%; III, 1%; IV, 0.5%), *BRIP1* (I-II, 1.2%), *ATM* (III, 1%; IV, 0.7%), *MSH6* (III, 1%; IV, 0.2%), and *TP53* (III, 1%; IV, 0.2%) among others. We did not observe significant differences in germlines alterations according to stage (all cases, p>0.05). Overall, incidental germline alterations were detected in 5% of bladder cancer patients regardless of stage.

CONCLUSIONS

- Patients with **bladder cancer** have similar rates of **potentially actionable mutations** and genomic landscapes **regardless of clinical disease stage**.
- **Incidental germline alterations** were detected in **5%** of bladder cancer patients, highlighting the benefit of **tumor/normal matched sequencing** in cancer subtypes that currently lack hereditary testing guidelines.
- These findings provide rationale for further investigating targeted therapies among early-stage bladder cancer patients.