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Comparing the somatic, germline, and immune landscapes of upper tract urothelial carcinoma (UTUC) and UC of the bladder (UCB).

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Background: Molecular characterization of anatomically distinct UCs has been limited by the rarity of UTUC; however, recent advances in real-world data curation have enabled larger UTUC cohort generation. Here, we investigated the somatic, germline, and immunologic landscapes of UTUC compared to UCB. **Methods:** From the Tempus Database, we retrospectively analyzed de-identified next-generation sequencing data from 505 UTUC (224 ureter, 281 renal pelvis) and 2,416 UCB cases (2,379 bladder, 37 urethra). Tumors were sequenced with the Tempus xT DNA and xR RNA assays. Pathogenic somatic mutations, immune cell infiltration predicted from gene expression patterns, TMB, PD-L1 from IHC, MSI, and mismatch repair (MMR) were evaluated. Incidental germline alterations were assessed in 46 genes for patients with tumor/normal-matched (T/N) sequencing (UTUC n=285, UCB n=1,359). Chi-squared, Fisher's exact, and Wilcoxon rank-sum tests were used to assess statistical significance ($p<0.05$, $q<0.05$ for false discovery rate correction for multiple testing). **Results:** Median age of the UTUC and UCB cohort were 73 and 70 years, respectively (p=0.003). The UCB cohort had significantly more males (75% vs 56%, $p<0.001$) and ever smokers (59% vs 46%, $p<0.001$).Alterations in *TERT*, *TP53*, *CDK12*, *RB1*, *ERBB2*, and *CDKN1A* were more frequent in UCB, while *KMT2D*, *FGFR3*, *BRIP1*, *CDKN2B*, *KRAS*, and *MYC* more frequent in UTUC (Table). Additionally, *FGFR3* fusions were more frequent in UTUC. Germline variants were found in 7.1% of UCB and 7.0% of UTUC cases, with trends towards higher prevalence of alterations in lynch-associated genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) in UTUC (0.6% vs 1.8%, p=0.059). The prevalence of TMB ≥ 10 mut/Mb was higher in UCB vs UTUC (17% vs 11%, $p<0.001$). UCB had increased PD-L1 positivity (p=0.013), whereas UTUC had more MSI-high (UTUC = 3.2% vs UCB = 1%, p=0.001) and deficient MMR (p=0.020) cases. There were similar proportions of total immune infiltrates in UCB and UTUC. However, UTUC harbored a higher percentage of CD4+ T cells ($p<0.001$), while UCB had a higher proportion of regulatory T and NK cells ($p<0.001$). **Conclusions:** Via comprehensive molecular characterization of UC, we observed distinct DNA alteration and tumor microenvironment patterns in UTUC and UCB. The germline results underline how T/N testing can identify patients with UTUC and/or UCB who can benefit from dedicated germline testing. Further research is warranted to elucidate the clinical implications of these findings. Research Sponsor: Tempus AI, Inc.

Molecular Characteristic	UCB (n = 2,416)	UTUC (n = 505)
TERT*	76%	52%
KMT2D*	22%	36%
RB1*	22.0%	8.9%
FGFR3*	13%	21%
CDK12*	5.0%	1.4%
TP53*	59%	51%
ERBB2*	14.0%	8.3%
***FGFR3* fusions**[†]	4.0%	6.1%

*% mutated, $q<0.05$; [†]$p<0.05$; [‡]$p< 0.001$; Analysis included short variants and copy number variants with the exception of *FGFR3* fusions.