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Genomic Biomarkers for the Prediction of Stage and Prognosis of Upper Tract Urothelial Carcinoma

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Abstract

Purpose—Genomic characterization of radical nephroureterectomy (RNU) specimens in patients with upper tract urothelial carcinoma (UTUC) may allow for thoughtful integration of systemic and targeted therapies. We sought to determine if genomic alterations in UTUC are associated with adverse pathologic and clinical outcomes.

Materials and Methods—Next-generation exon capture sequencing of 300 cancer-associated genes was performed in 83 patients with UTUC. Genomic alterations were assessed individually and also grouped into core signal transduction pathways or canonical cell functions for association with clinicopathologic outcomes. Binary outcomes, including grade (high vs. low), T stage (pTa/T1/T2 vs. pT3/T4), and organ-confined status (pT2 and N0/Nx vs. >pT2 or N+) were assessed with Kruskal-Wallis test and Fisher's exact test as appropriate. Associations between alterations and survival were estimated using the Kaplan-Meier method and Cox regression.

Results—Of the 24 most commonly altered genes within 9 pathways, *TP53/MDM2* alterations and *FGFR3* mutations were the only two alterations uniformly associated with high-grade, advanced stage, non-organ-confined disease, recurrence-free survival, and cancer-specific survival. *TP53/MDM2* alterations were associated with adverse clinicopathologic outcomes whereas *FGFR3* mutations were associated with favorable outcomes. We created a risk score using *TP53/MDM2* and *FGFR3* status that was able to discriminate between adverse pathologic and clinical outcomes, including in the subset of patients with high-grade disease. The study is limited by small numbers and lack of validation.

Conclusions—Our data indicate that specific genomic alterations in RNU specimens correlate with tumor grade, stage, and cancer-specific survival outcomes.

Keywords

upper tract urothelial carcinoma; genomics; prediction; biomarkers; TCC

Introduction

Currently available prognostic tools that utilize clinical and pathological variables are limited for upper tract urothelial carcinoma (UTUC). In UTUC predictive models, utilization of pre-operative parameters results in only 76% accuracy for identifying non-organ-confined disease (1). Post-operative nomograms incorporating complete pathologic information are also limited (2-5). Biomarker analysis of pathologic specimens may allow for enhanced risk-stratification and subsequent treatment with either conventional or targeted systemic therapies (6, 7).

Knowledge of the mutation profile of bladder UC has flourished with publication of The Cancer Genome Atlas (TCGA) Research Network's work and other studies (8, 9). The genomic landscape of UTUC is less clear. Recently, our group published a comparative genomic analysis of UTUC and bladder UC (10). This work demonstrates that the types of mutations found in invasive bladder and upper tract tumors are similar, but the mutational frequency is quite different. Specifically, *TP53* and *RBI* mutations were less common in UTUC while *FGFR3* mutations were more common in invasive UTUC. The clinicopathologic relevance of the mutations identified in UTUC is yet to be fully explored but may provide rationale for improved risk-stratified management approaches including organ-sparing strategies and integration of tailored therapeutics.

Herein, we examine the association between genomic alterations and clinicopathologic outcomes in patients with UTUC treated with radical nephroureterectomy (RNU).

Materials and Methods

This investigation was undertaken with Institutional Review Board authorization. The study population included clinically localized patients treated with RNU for UTUC between 11/1995-1/2014 with tissue available in the institutional biorepository (n=83). Lymph node dissection was performed at the operating surgeon's discretion. In general, perihilar lymph nodes, para-/pre-caval (right-sided tumors) or pre-/para-aortic (left-sided tumors), and

ipsilateral common iliac lymph nodes were removed. For distal ureteral tumors, ipsilateral pelvic lymph node dissection was performed. A representative H&E slide was reviewed by a board-certified genitourinary pathologist to confirm histology, grade, and stage; slides with tumor content >70% were selected for DNA extraction.

Each patient was followed every 3-4 months in the first post-operative year, semiannually for the second year, and then at least annually. Evaluation included history and physical, laboratory evaluation including urinary cytology, cross-sectional imaging of the abdomen and pelvis, and imaging of the chest. Adjuvant chemotherapy was discussed for patients with non-organ-confined disease; specific regimens were individualized based on renal function and performance status. Bladder recurrences were not considered as distant recurrences. Tumor histology was assessed with World Health Organization classification and criteria. The 2010 AJCC TNM staging system was employed.

Targeted capture-based next-generation sequencing (Memorial Sloan Kettering Integrated Mutation Profiling of Actionable Cancer Targets, MSK-IMPACT) to identify somatic mutations and copy number alterations was performed on all specimens (10, 11). Pre-specified genomic alterations deemed to have functional significance were analyzed. For known oncogenes, we included recurrent point mutations and amplifications. For putative tumor suppressors, we included truncating mutations (nonsense, frameshift indels) and deletions.

Statistical Analysis

Patient and disease characteristics were tabulated as a whole and by grade. One patient with an ultramutated tumor (422 mutations) due to an activating *POLE* mutation was excluded since most mutations were likely passenger events. Binary outcomes of interest included T stage (pTa/T1/T2 vs. pT3/T4), grade (high vs. low), and organ-confined status (pTa/T1/T2 & pN0/Nx vs. pT3/T4 or pN+). We compared mutation frequencies by binary outcomes using Fisher's exact test. Mutations were assessed individually and also grouped into core signal transduction pathways or canonical cell functions (Supplementary Table 1). Associations between mutations and survival were estimated using the Kaplan-Meier method and Cox regression.

All analyses were conducted in R version 3.1.1 (R Core Development Team, Vienna, Austria) including the 'survival' package. Genomic and associated clinicopathologic data are publically available through the MSKCC cBioPortal for Cancer Genomics (12).

Results

Patient and tumor characteristics are presented in Table 1. The median age was 68 years and the majority of patients were male (65.9%). High-grade disease was present in 72% of patients. Overall, 61/82 (74.4%) of patients received a lymph node dissection. The median number of lymph nodes removed was 8 (range 1-36). Neoadjuvant chemotherapy was administered to 8.5% of patients while 34.1% received post-operative chemotherapy. Median follow-up time among survivors was 3.2 years (range 0.1-17.3). During follow-up, 24 patients died, 23 patients died from disease, and 31 patients experienced a distant recurrence.

Median survival time was not reached; however, the survival probability (95% CI) was 0.94 (0.88, 0.99) at 1 year and 0.64 (0.52, 0.79) at 5 years.

Pathologic Outcomes

On univariable analysis, mutations in *TP53* ($p=0.008$), *FGFR3* ($p<0.001$), the RTK/Ras/MAPK pathway ($p=0.001$), *CREBBP* ($p=0.04$), *KMT2C* ($p=0.02$), and *STAG2* ($p=0.006$) were significantly associated with grade (Supplementary Table 2). Patients with mutations in *TP53* and the RTK/Ras/MAPK pathway had a higher frequency of high-grade disease whereas patients with mutations in *FGFR3*, *CREBBP*, and *STAG2* had a higher frequency of low-grade disease. Mutations in *TP53* ($p=0.002$), *CCND1* ($p=0.046$), *FGFR3* ($p<0.001$), *ERBB2* ($p=0.046$), *ERBB3* ($p=0.046$), *KRAS* ($p=0.016$), and *STAG2* ($p=0.013$) were significantly associated with tumor stage. Patients with mutations in *TP53*, *CCND1*, *ERBB2*, *ERBB3*, and *KRAS* had a higher frequency of pT3/T4 disease whereas patients with mutations in *FGFR3* and *STAG2* had a higher frequency of pTa/T1/T2 disease. When limiting our analyses to the 59 patients with high-grade disease, only *TP53/MDM2* ($p=0.029$) and *FGFR3* ($p=0.015$) remained significantly associated with tumor stage. *TP53* mutation and *MDM2* amplification (*TP53/MDM2* alteration) were considered jointly as they were mutually exclusive events and *MDM2* amplification is known to functionally inactivate *TP53* through ubiquitination, nuclear export, and transcriptional regulation (13).

Mutations in *TP53* ($p=0.003$), *CCND1* ($p=0.048$), *FGFR3* ($p<0.001$), *KRAS* ($p=0.018$), and *STAG2* ($p=0.012$) were significantly associated with organ-confined status. Patients with mutations in *STAG2* and *FGFR3* had a higher frequency of organ-confined disease whereas patients with mutations in *KRAS*, *TP53*, and *CCND1* had a higher frequency of non-organ-confined disease. When analyzing the 59 patients with high-grade disease, only *FGFR3* ($p=0.034$) was significantly associated with organ-confined disease.

Survival Outcomes

Mutations in *TP53* (HR 3.13, 95% CI 1.44-6.80, $p=0.002$), *TP53/MDM2* alteration (HR 3.66, 95% CI 1.77-7.57, $p<0.001$), *CCND1* alteration (HR 5.19, 95% CI 2.04-13.22, $p<0.001$), and *ERBB3* mutations (HR 3.93, 95% CI 1.18-13.10, $p=0.016$) significantly increased the risk of distant recurrence. Mutations in *FGFR3* (HR 0.15, 95% CI 0.06-0.37, $p<0.001$), RTK/Ras/MAPK pathway (HR 0.39, 95% CI 0.19-0.79, $p=0.006$), *KMT2C* (HR 0.29, 95% CI 0.09-0.94, $p=0.029$), and *STAG2* (HR 0.22, 95% CI 0.05-0.92, $p=0.022$) significantly decreased the risk for distant recurrence. In the 59 high-grade patients, *TP53/MDM2* ($p=0.048$), *CCND1* ($p=0.011$), and *FGFR3* ($p=0.012$) were still significantly associated with distant recurrence.

Mutations in *TP53* (HR 3.25, 95% CI 1.29-8.21, $p=0.008$), *TP53/MDM2* alteration (HR 3.43, 95% CI 1.46-8.08, $p=0.003$), and *CCND1* alteration (HR 3.50, 95% CI 1.14-10.72, $p=0.02$) significantly increased the risk of death from disease whereas *FGFR3* mutation (HR 0.22, 95% CI 0.08-0.60, $p=0.001$) significantly decreased the risk of death from disease (Supplementary Table 3). Note that there were no recurrences or deaths from disease among low-grade patients, so we could not adjust these analyses for grade. When we adjusted for stage, only *SMARCA4* was significantly associated with death from disease ($p=0.024$). In

the 59 patients with high-grade disease, only *SMARCA4* was significantly associated with death from disease ($p=0.021$).

Risk Score

Of the 30 most commonly mutated genes within 9 genomic pathways, *TP53/MDM2* pathway alterations and *FGFR3* mutations were the only two alterations uniformly associated with high-grade, advanced stage, non-organ-confined disease, recurrence-free survival, and cancer-specific survival. *TP53/MDM2* alterations were associated with adverse clinicopathologic outcomes whereas *FGFR3* mutations were associated with favorable outcomes. Fifteen patients (18.3%) had *TP53* mutations, 6 (7.3%) had mutually exclusive *MDM2* amplifications, and 43 (52.4%) had *FGFR3* mutations (Supplementary Table 1).

We created a risk score including *TP53/MDM2* and *FGFR3* based on these data. The risk score was assigned as follows: 0=normal *TP53/MDM2* and altered *FGFR3*, 1=normal *TP53/MDM2* and normal *FGFR3*, 2=altered *TP53/MDM2* and normal *FGFR3*. While there was not a significant interaction between the two genes with respect to any of the outcomes of interest, after examining associations between a 4-level categorical risk score and the outcomes of interest, the group with mutations in both genes did not have similar parameter estimates to the group without mutations in either gene. In other words, patients that had both altered *TP53/MDM2* and *FGFR3* were not considered to be a separate risk group or considered in the intermediate risk group. Therefore, 3 patients who had mutations in both genes were excluded from analysis, leaving 79 patients in the risk score analysis. Notably, one of the patients with mutations in both *TP53* and *FGFR3* had Lynch Syndrome with documented microsatellite instability and a hypermutated sample. The other two patients had *FGFR3* mutations (S249C, Y373C) concomitant with *MDM2* amplification. We treated the risk score as an ordinal variable, which assumes that there is equal increase in risk moving from low to intermediate risk and from intermediate to high risk.

Table 2 illustrates the association with risk score and pathologic variables. On univariable logistic regression, risk score was significantly associated with grade ($p=0.002$), stage ($p<0.001$), and organ-confined status ($p<0.001$). When we limit to high-grade patients, risk score remained significantly associated with stage (OR 3.01, 95% CI 1.41-6.40, $p=0.004$) and organ-confined status (OR 2.62, 95% CI 1.26-5.44, $p=0.01$). These associations also held among high-grade patients after adjusting for location of tumor.

Increasing risk score was associated with both worse recurrence-free and cancer-specific survival (Figures 1 and 2). On univariable Cox regression, limited to high-grade patients, risk score was marginally associated with cancer-specific survival (HR 1.76, 95% CI 1.00-3.11, $p=0.05$) and remained significantly associated with recurrence (HR 1.95, 95% CI 1.21-3.12, $p=0.006$). On multivariable analysis, these associations also held among high-grade patients after adjusting for location of tumor (**Supplementary Table 4**).

Discussion

We identified prognostic genetic alterations and potential therapeutic targets in patients with UTUC by utilizing next-generation sequencing. We found several genetic alterations that are

associated with adverse clinicopathologic outcomes, including *TP53* mutation and *MDM2* amplification. Conversely, *FGFR3* mutations were associated with favorable outcomes. By combining the presence or absence of *TP53/MDM2* alterations and *FGFR3* mutations, we developed a risk score with a biologic basis that supports the divergent pathway hypothesis of urothelial tumorigenesis (14). *FGFR3* mutations, which are generally associated with non-invasive, indolent tumors, are identified in up to 80% of Ta tumors whereas the rate of *FGFR3* mutations in muscle-invasive tumors is low (10-20%). *TP53* mutations are rare in low-grade tumors but common in invasive and metastatic urothelial carcinomas (14, 15). Importantly, the risk score was able to provide discriminatory information even amongst the subgroup of patients with high-grade disease. We identified a significant proportion of patients (36%) with high-grade UTUC that harbored *FGFR3* mutations, which is substantially higher than the bladder TCGA (12%) (8). While our population was heavily represented by high-grade tumors, many of these were non-muscle-invasive, in contrast to the bladder TCGA that only sequenced T2-T4 tumors. This potentially suggests that in UTUC, some proportion of high-grade tumors progress from low-grade, *FGFR3*-mutated tumors instead of arising as high-grade tumors through a de novo, divergent pathway (i.e., *TP53*- or *RB*-mutated) (14). In the context of the present study, an *FGFR3*-mutated high-grade tumor may be one that ultimately demonstrates a less aggressive clinical course.

Our data has several applications if sequencing is performed on RNU specimens. For instance, patients with high-risk (*TP53/MDM2*-altered tumors) may be considered for more rigorous surveillance protocols, adjuvant chemotherapy, and selective enrollment into clinical trials. Admittedly, the opportunity to intervene once RNU has been performed is limited since many patients will be ineligible for cisplatin-based chemotherapy and those patients that recur will nearly uniformly die from their disease (16).

A molecular profiling approach for UTUC would be most useful if it could be performed in the pre-operative setting, whereby high/low-risk patients could be identified prior to RNU. Staging limitations generally mandate RNU as the standard treatment for high-grade disease. RNU may overtreat patients with lower stage disease. Conversely, patients with advanced disease who may benefit from neoadjuvant chemotherapy are often not identified prior to surgery. With this in mind, we have employed the MSK-IMPACT assay on ten specimens obtained from ureteroscopic biopsy specimens (unpublished data). For the ureteroscopic biopsy samples, DNA quantity and quality were sufficient for next-generation sequencing in all samples. Further, hotspot mutations reported in the bladder TCGA were identified in all samples. We are also in the process of performing targeted sequencing on paired biopsy/RNU specimens to assess concordance in a proof-of-concept study. Genomic sequencing in the pre-RNU space from biopsy material could potentially serve as a surrogate for clinical staging and prognostication while also identifying candidates for appropriate organ-sparing options, **performance and extent of lymphadenectomy**, or targeted therapy in the neoadjuvant setting.

There are several limitations to our study. Although our follow-up was relatively short, population-based analyses suggest that the majority of cancer-specific deaths (87%) take place within 3 years of RNU (4). The sample size was small, limiting our ability to detect incremental differences in outcomes or perform useful subgroup analyses. For instance, we

could not examine potential predictors of response to chemotherapy based on the small numbers. It is also possible that the administration of neoadjuvant chemotherapy to a minority of patients may have potentially biased the mutations that were identified in those particular patients. Similarly, we were not able to adjust for stage among high-grade patients due to the small sample size. In our multivariable analysis, we elected to incorporate variables that are potentially available in the preoperative setting, so we did not include stage. Important clinicopathologic variables such as lymphovascular invasion and tumor architecture were not uniformly collected for each specimen and were also omitted from multivariable analyses and associations with genetic alterations.

Nevertheless, we did find that our risk score provided discriminatory information for patients with high-grade disease. Further, our patient population was enriched for patients with high-grade disease, but this likely represents the group most likely to benefit from individualized therapy. Given the relative paucity of data regarding genomic biomarkers in UTUC, we employed a discovery approach and did not adjust for multiple testing. As such, our results must be interpreted as exploratory and subject to false discovery, therefore they all require validation in future studies. We were not able to sequence consecutive RNU specimens due to frozen tissue availability; however, MSK-IMPACT is now available for paraffin-embedded tissues. Our findings have also not yet been prospectively or externally validated.

Conclusions

Our data indicate that specific patterns of genomic alterations in RNU specimens correlate with tumor grade, stage and cancer-specific survival outcomes. This information appears to provide valuable prognostic data in regard to risk stratification for patients with UTUC that could be used to offer better individualized treatment strategies, particularly if available in the pre-operative setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Recurrence-free survival of 82 patients with upper tract urothelial carcinoma treated with radical nephroureterectomy stratified by genomic biomarker risk score.

Figure 2. Cancer-specific survival of 82 patients with upper tract urothelial carcinoma treated with radical nephroureterectomy stratified by genomic biomarker risk score.

Table 1

Descriptive characteristics of 82 upper tract urothelial carcinoma patients treated with radical nephroureterectomy genomically profiled with MSK-IMPACT.

Variable	No (%)
Age, median (range), years	68 (38, 88)
Gender	
Male	54 (65.9%)
Female	28 (34.1%)
Smoking	
Never	21 (25.6%)
Quit	45 (54.9%)
Current	16 (19.5%)
History of Bladder cancer	
No	50 (61%)
Yes	32 (39%)
Laterality	
Right	48 (58.6%)
Left	34 (41.4%)
Grade	
Low	23 (28.0%)
High	59 (72.0%)
Tumor Site	
Renal Pelvis	43 (52.4%)
Renal Pelvis and Ureter	26 (31.7%)
Ureter	13 (15.9%)
T Stage	
pTa/Tis	29 (35.4%)
pT1	15 (18.3%)
pT2	8 (9.8%)
pT3	23 (28.0%)
pT4	7 (8.5%)
N stage	
pN+	17 (20.7%)
pN0	44 (53.7%)
pNx	21 (25.6%)
Organ-Confined	
No	31 (37.8%)

Variable	No (%)
Yes	51 (62.2%)
Surgical margins	
Negative	71 (86.6)
Positive	11 (13.4%)
Chemotherapy	
None	49 (59.8%)
Neoadjuvant	7 (8.5%)
Adjuvant	3 (3.7%)
Salvage	25 (30.4%)

Table 2

Association of genomic biomarker risk score and pathology features.

	Prognostic Marker Score			
	Favorable	Intermediate	Unfavorable	P value *
Patients	40	21	18	
High-Grade Disease	18 (45.0%)	20 (95.2%)	18 (100.0%)	0.002
T Stage >pT2	5 (12.5%)	10 (47.6%)	14 (77.8%)	<0.001
N Stage				
N0/Nx	35 (87.5%)	15 (71.4%)	12 (66.7%)	0.058
N+	5 (12.5%)	6 (28.6%)	6 (33.3%)	
Non-Organ-Confined Disease[#]	6 (15.0%)	10 (47.6%)	14 (77.8%)	<0.001

* P values from logistic regression treating prognostic marker score as an ordinal variable.

[#] Non-organ-confined disease defined as >pT2 and/or N+.