HHS Public Access

Author manuscript

Curr Urol Rep. Author manuscript; available in PMC 2016 April 07.

Published in final edited form as:

Curr Urol Rep. 2016 February ; 17(2): 12. doi:10.1007/s11934-015-0566-y.

Prognostic genetic signatures in upper tract urothelial carcinoma

Qiang Li, **Aditya Bagrodia**, **Eugene K. Cha**, and **Jonathan A. Coleman**

Urology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

Abstract

Urothelial carcinoma is a highly heterogeneous disease that can arise throughout the entire urothelial lining from the renal pelvis to the proximal urethra. Upper tract urothelial carcinoma (UTUC) is rare and while it shares many similarities with urothelial carcinoma of bladder (UCB), there are also significant differences between UTUC and UCB regarding clinical management and outcomes. No major advances have been made recently in the development of new systemic therapies for urothelial carcinoma, partly due to the lack of understanding of underlying molecular pathogenetic mechanisms. In the past decade, the emergence of next-generation sequencing has greatly enabled genomic characterization of tumor samples. Researchers are currently exploring a personalized approach to augment traditional clinical decision-making based on genetic alterations. In the present review, we summarize current genomic advances in UTUC and discuss the potential implications of these developments for developing prognostic and predictive biomarkers.

Keywords

upper tract urothelial carcinoma; genomics; prediction; biomarkers

Introduction

Upper tract urothelial carcinoma (UTUC) can arise from the epithelial lining of the urinary tract from the renal calyces to the ureteric orifices. Compared to urothelial carcinoma of bladder (UCB), UTUC is a rare disease, accounting for approximately 5–10% of all urothelial carcinomas and less than 10% of renal tumors [1]. UTUC may be associated with smoking, arsenic exposure, analgesic abuse, occupational carcinogen exposure, hypertension, long-standing urinary obstruction, infection and Balkan nephropathy. Radical nephroureterectomy (RNU) with excision of the bladder cuff is the gold standard treatment for organ-confined disease. Some patients with low-risk disease may be treated with endoscopic ablation or segmental resections.

Current knowledge about the risk stratification and molecular pathogenesis of UTUC is sparse and often extrapolated from UCB, which is thought to share common pathways of

Corresponding Author: Jonathan A. Coleman, M.D., Urology Service, Department of Surgery, Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan Kettering Cancer Center, 353 E. 68th Street, New York, NY 10065, Tel: 646-422-4432, Fax: 212-452-3323, colemanj@mskcc.org.

carcinogenesis. UTUC however presents distinct challenges given limitations in accurate pathologic grading and staging at diagnosis with current endoscopic biopsy techniques and imaging technologies. Specifically, decision-making and the prognosis of UTUC relies heavily on TNM stage and pathological grade that is not accurately available until RNU is performed, at which point a significant proportion of patients may be rendered ineligible for adjuvant cisplatin-based chemotherapy. A personalized approach for prediction of oncologic outcomes and therapeutic responses is important, given the variability in disease behavior, the diversity of treatment options, and their impact on kidney function and quality of life. Further understanding of the genetic mechanisms underlying the development of UTUC will certainly help identify biological markers for prognostication and potential therapeutic targets. Intense research efforts are being made to identify and characterize robust molecular and genetic markers. Novel genomic technologies, such as next-generation sequencing, have improved our understanding of the molecular basis of both UCB and UTUC. In this review, we focus on the topic of genetic alterations in UTUC and the value of prognostic genetic markers in the prediction of outcomes and possible response to various therapeutic interventions.

1. Chromosomal aberrations and copy number variation

Comparative genomic hybridization has been used to identify chromosomal aberrations in UTUC. Losses in 9q are present in 50% of cases and high level amplifications are often detected at 1q21~q25, 6p22~p23, 8q21~q22, 8q22~q24.1, 11q13, and 12q14~q21 [2]. One study utilized array-based comparative genomic hybridization to detect frequent copy number gains on chromosomal regions 8p23.1 and 20q13.12, and frequent copy number losses on chromosomal regions 13q21.1, 17p13.1, 6q16.3, and 17p11.2. DNA copy number aberrations occurred more frequently in tumors with lymphovascular invasion (LVI) than in those without LVI [3]. In a cohort of 171 UTUC patients treated with RNU, Sasaki et al. demonstrated 18% (31/171) *ERBB2* gene amplification using dual-color in situ hybridization. *ERBB2* gene amplification was correlated with HER2 protein overexpression and high-grade histology. HER2 positivity was found to be an independent predictive marker for early intravesical recurrence of urothelial carcinoma [4]. Recently, we examined the landscape of copy number alterations (CNAs) in UTUC and found that *TP53*/*MDM2*-altered UTUC tumors possessed a high frequency of CNAs. *TP53*/*MDM2*-altered high-grade invasive UTUC tumors had significantly more copy number gains and total CNAs compared with *FGFR3*/*HRAS*/*KRAS* mutant high-grade invasive UTUC tumors. Furthermore, high-grade tumors had more CNAs than low-grade tumors, and invasive tumors had more CNAs than non-invasive tumors [5**].

2. Microsatellite instability

Epidemiological studies have demonstrated a 14-fold increased incidence of developing UTUC and a cumulative lifetime risk of 2.9% in hereditary non-polyposis colorectal cancer (HNPCC) patients compared to general population [6]. HNPCC, also known as Lynch syndrome (LS), is an autosomal-dominant familial cancer syndrome caused by germline mutations in the DNA mismatch repair (MMR) genes. LS patients with *MSH2* mutations are at an increased risk for not only UTUC, but also UCB [7]. The MMR genes comprise

MLH1, *PMS1*, *PMS2*, *MSH2*, *MLH3*, and *MSH6*. Defective MMR function leads to replication errors and frame shift mutations, which may result in aberrations in major cancer gene pathways. Loss of function in the MMR system results in microsatellite instability (MSI) throughout the human genome. MSI is a hallmark feature seen in approximately 85% of LS-associated tumors in mutation carriers [8]. An early study indicated a high level of MSI (46%) in UTUC [9]. High MSI indicates a better prognosis, especially in patients younger than 70 years with stage T2-T3N0M0 compared to low MSI patients [10]. MSI may arise from inactivating germline mutations, *MLH1* promoter hypermethylation (10% of sporadic cases of UTUC) [11], or overexpression of upstream miR-155 [12]. García-Tello et al. recently found that the inactivation of *PMS2* or *MLH1* occurs in a quarter of sporadic UTUC cases and is an independent marker of good prognosis [13].

Interestingly, a recent phase 2 study showed that mismatch repair status predicted clinical benefit of immune checkpoint blockade with pembrolizumab [14]. Pembrolizumab was administered intravenously in patients with mismatch repair-deficient colorectal cancers and in patients with mismatch repair-proficient colorectal cancers. The study showed mismatch repair-deficient colorectal cancer patients had significantly better immune-related objective response rate and immune-related progression-free survival rate compared with mismatch repair-proficient colorectal cancer patients. The prolonged progression-free survival in mismatch repair-deficient colorectal cancer patients was associated high somatic mutation loads (a mean of 1782 somatic mutations per tumor in mismatch repair-deficient tumors, as compared with 73 in mismatch repair-proficient tumors). The results from this study suggest the potential utility of immune checkpoint inhibitors in a specific subset of UTUC tumors based on mismatch repair genetic status [14].

3. Mutational landscape and clinically relevant genes

Recently, we comprehensively characterized the spectrum of genomic alterations in UTUC using massively parallel next-generation sequencing [5**]. The most frequently mutated genes in UTUC tumors included those commonly altered in previous studies of urothelial carcinoma of the bladder (UCB), including *FGFR3* (54%), *KMT2D* (35%), *KDM6A* (34%), *STAG2* (22%), *CDKN2A* (21%), *TP53* (18%), *PIK3CA* (16%) and *TSC1* (16%) (Figure 1). Consistent with prior studies, we identified a predominantly mutually exclusive pattern of alterations in the RTK/RAS/MAPK pathway and the p53/MDM2 pathway. The prevalence of specific mutations differed between UTUC and UCB. *FGFR3*, *HRAS* and *CDKN2B* were more frequently altered in UTUC tumors (36.8% vs 21.6%, p=0.042; 14.0% vs. 1.0%, p=0.001; and 15.8% vs. 3.9%, p=0.014, respectively) whereas *TP53* and *ARID1A* were more frequently altered in UCB tumors (57.8% vs. 24.6%, p<0.001 and 27.5% vs. 12.3%, p=0.029, respectively) [5**].

1) p53

The tumor suppressor gene *TP53* has been described as “the guardian of the genome” due to its role in conserving stability by preventing genome mutation. Mutations of p53 have been identified in approximately 50% of all human cancers. p53 can activate DNA repair genes to repair DNA damage or can arrest cell growth at the G1/S checkpoint. p53 can initiate apoptosis if DNA damage proves to be irreparable. Among all biomarkers, p53 expression is

the most extensively investigated molecular marker in UTUC. Expression of mutant p53 has been found approximately 30–60% of UTUC [15*]. Many studies have demonstrated a correlation between p53 expression and poor survival. In immunohistochemistry (IHC) studies, p53 often lost statistical significance in multivariable analysis or failed to confirm other well established pathologic prognostic markers in multivariable analysis.

The initial p53 IHC study examined the prognostic role of p53 expression in 83 UTUC patients. The authors showed that the overexpression of p53 was significantly associated with tumor aggressiveness and worse patient survival [16]. Tumor stage, grade, and p53 expression were all significantly associated with outcomes on univariate analyses. However, tumor grade was not an independent predictor in a multivariable analysis whereas p53 expression status remained significant. A Japanese single-center study (n = 66) [17] and a European single-center study (n = 53) [18] showed p53 was a prognostic factor in univariable analyses but did not emerge as an independent prognostic factor after adjustment for clinical and pathologic characteristics. The most recent IHC study examined p53 expression in 112 UTUC patients and found high p53 expression was an independent predictor of poor progression-free (hazard ratio [HR] =3.74, p=0.025) and cancer-specific (HR=5.87, p=0.030) survival [19].

Other investigators have studied p53 protein expression and DNA mutation analysis simultaneously, albeit with only a minority of patient samples suitable for sequencing analysis. The first sequencing study of *TP53* point mutations in exons 4 through 9 in UTUC demonstrated *TP53* mutations in 7 of 26 cases, 6 of which were also positive for p53 expression. Overexpressed p53 was frequently detected in invasive and high-grade tumors [20]. Another study identified p53 point mutations in 6 of 21 cases, 5 of which were positive for p53 protein expression [21]. Bagrodia et al. prospectively evaluated the utility of a tissue biomarker panel of cell cycle regulators (p53, p21, p27, cyclin E) and a proliferative marker (Ki-67) in patients with UTUC treated with RNU [22]. The number of altered biomarkers was categorized as favorable (≤2 altered markers) or unfavorable (> two altered markers). An unfavorable tissue biomarker score was associated with advanced pathologic T stage, non-organ-confined disease, LVI, and inferior cancer-specific survival in RNU patients.

2) FGFR3

Fibroblast growth factor receptor 3 (FGFR3) is expressed in normal urothelium. Mutation of *FGFR3* in bladder cancer is strongly associated with low tumor grade and stage. van Oers et al. examined *FGFR3* mutations using the SNaPshot method. They found that *FGFR3* mutations occurred with the same frequency in bladder (48%) and UTUC (46%). *FGFR3* mutations were associated with low-stage tumors and a milder disease course in UTUC and invasive UTUCs with *FGFR3* mutations have a more favorable prognosis [23]. Recently, Lyle et al. identified *FGFR3* mutations in 40% of UTUC tumors using real-time polymerase chain reaction. *FGFR3* mutations were predominantly associated with non-invasive tumors and overall better survival compared with tumors with wild-type *FGFR3* [24].

In our genomic landscape study of UTUC, fifteen patients (18.3%) had *TP53* mutations, 6 (7.3%) had mutually exclusive *MDM2* amplifications, and 43 (52.4%) had *FGFR3* mutations [5]. Mutation 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* (HR 5.19, 95% CI 2.04–13.22, p<0.001), and *ERBB3* (HR 3.93, 95% CI 1.18–13.10, p=0.016) significantly increased the risk of distant recurrence after RNU whereas mutation 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 (Table 1). *TP53*/*MDM2* alterations were associated with adverse clinicopathologic outcomes whereas *FGFR3* mutations were associated with favorable outcomes. 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*. 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 limited our analyses 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 (Table 1). 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).

4. Single nucleotide polymorphisms (SNP)

Researchers from Taiwan have performed molecular epidemiological studies to evaluate the single nucleotide polymorphism of different genes in UTUC. Lin et al. examined the cyclin D1 (*CCND1*) genotypes of 170 patients and 249 control subjects. They found that C allele of the cell cycle regulator *CCND1* C1722G polymorphism may be a potential predictive and prognostic biomarker for advanced UTUC [25]. Chang et al. examined six *CAV1* polymorphic genotypes, *C521A (rs1997623), G14713A (rs3807987), G21985A (rs12672038), T28608A (rs3757733*), T29107A (rs7804372), and *G32124A (rs3807992)* in 218 UTUC patients and 580 healthy controls using polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP). The haplotype analysis showed the A allele of *CAV1 rs3807987* and T allele of *CAV1 rs7804372* might become potential biomarkers for the early screening and risk prediction of UUTC [26]. Another group from France demonstrated an association between a T/T rs9642880 genotype on chromosome 8q24 and aggressive UTUC tumors [27]. Recently, the G allele of COX2 G-765C and A allele of COX2 intron 5 were found to be genomic risk factors predictive biomarkers for UTUC in Taiwan [28]. Although these SNP studies have suggested that information regarding genetic variation may improve risk prediction, they are probably not sufficient to identify all potentially causative SNPs and to develop a full understanding of these genetic variations in UTUC.

5. Epigenetic biomarkers

Epigenetic changes affect the spatial conformation of DNA and its transcriptional activity and lead to changes in phenotype without changing the sequence of DNA bases. Researchers

have observed that many tumors show an aberrant epigenetic modification pattern, affecting a variety of cancer-related genes. Epigenetic regulation occurs on several mechanistic levels, including DNA methylation, covalent histone modifications, and small regulatory RNAs [29]. In our cohort of UTUC tumors profiled with next-generation sequencing, mutations in chromatin-modifying genes (CMGs) were highly prevalent in UTUC (*KDM6A* 34%, *ARID1A* 12%, *KMT2D* 35%, *CREBBP* 16%) (Figure 1) [5**].

Promoter methylation of tumor suppressors is a frequent and early event in tumor development. Aberrant promoter hypermethylation has been investigated in different panels of genes in UCB, including tumor suppressor genes, oncogenes, genes involved in cell adhesion, and genes of cell cycle regulation [30]. Promoter methylation was first demonstrated in 86% of urothelial carcinomas and occurred both more frequently and more extensively in UTUC (94%) than in bladder tumors (76%). Methylation was associated with advanced tumor stage and higher tumor progression and mortality rates, when compared with tumors without methylation. Methylation at the *RASSF1A* and *DAPK* loci, in addition to tumor stage and grade, was associated with disease progression [11]. Importantly, DNA methylation assays can be performed on small biopsies, archival frozen or paraffin-embedded samples, as well as on the soluble genomic DNA found in peripheral blood and voided urine samples. A panel of epigenetic biomarkers (*GDF15*, *TMEFF2* and *VIM* promoter methylation) was tested in 57 UTUC tumors, 36 normal upper tract urothelial samples, 22 urines from UTUC patients and 20 urines from controls. This panel identified UTUC with 100% and 91% sensitivity in tissue and urine samples, respectively, and 100% specificity in both samples. Low *VIM* promoter methylation levels independently predicted poor disease-specific survival in UTUC patients [31].

Xiong et al. conducted methylation-sensitive polymerase chain reaction for the promoter regions of ten genes (*ABCC6*, *BRCA1*, *CDH1*, *GDF15*, *HSPA2*, *RASSF1A*, *SALL3*, *THBS1*, *TMEFF2*, and *VIM*) in 687 UTUC patients to correlate methylation status with prognosis. Among ten genes, only methylated *TMEFF2* promoter and *BRCA1* promoter were significantly associated with CSS [32]. Although aberrant DNA methylation patterns in UTUC have emerged as potential biomarkers that are detectable in the serum or voided urine of UTUC patients, none have been validated, nor have they reached a sufficient level of accuracy. Clinically relevant methylation assays still await more validation studies, testing on large cohorts of patients and healthy controls, and functional validation of aberrant methylation patterns.

6. Potential biomarkers from gene expression profiling

Most previous biomarker studies in UTUC have focused on immunohistochemical analysis of protein expression. Numerous studies investigated the prognostic impact of various tissue-based molecular markers that are related to cellular processes such as cell adhesion (Metalloproteinase-9, E-cadherin [33], ParvB [34], snail [35], b-catenin[36]), cell signaling (EGFR[37], EMP3 [38], HER2 [4], PI3K/AKT [39, 40], IGFBP-5 [41], mTOR [42]), angiogenesis (Hypoxia-inducible factor-1[43]), cell proliferation (Ki67[44], p27 [45],cyclin D[46], NF- κ B [47], Aurora-A[48]), cell transport (GRP78 [49]) and apoptosis (bcl-2, survivin [50]). Recently, Wu et al. compared the genome-wide mRNA expression profile

using digital gene expression sequencing of tumors and matched normal tissues in 10 UTUC patients. They identified 3431 to 7702 significantly deregulated genes, mainly characterized by abnormal cell proliferation, and metabolism. Further IHC study showed that low protein expression of ALDH2 and high CCNE1/SMAD3 were associated with lower overall survival in a cohort of 103 patients [51]. Comparative proteomic analysis of urine has recently been applied in UTUC. Lu et al. identified 55 differential proteins among totally 1028 protein spots in the urine of 13 UTUC patients compared with the urine of 20 healthy control adults using two-dimensional gel electrophoresis. Three proteins (CALR, annexin A2 and annexin A3) were found to be essential secreting proteins in the urine from UTUC tumor tissues, suggesting their potential role as a panel of biomarkers [52]. However, the major limitations shared by these studies were their retrospective nature and small sample sizes.

7. Implication of genomics in UTUC: Potential therapeutic targets and prediction of response

Major advances have recently been made in contributing to the understanding of the genetics underlying the potential pathogenesis of both UCB and UTUC. These advances may lead to identification of new biomarkers and potential therapeutic targets for UTUC. In the near future, personalized genetic profiling of primary or metastatic tumor cells may become readily available for routine clinical decision-making, potentially allowing for identification of patients that are likely to respond to systemic therapy [53]. Our recent genomic study not only revealed the molecular landscape of UTUC, but also identified several currently targetable genetic changes in oncogenic pathways of UTUC, such as *FGFR3* (54% mutated), *CDKN2B* (21% altered), *TSC1* (16% altered), and *PIK3CA* (15% altered). Researchers may shift the focus of investigation from chemotherapy to targeted therapies, either in combination with cytotoxic agents, or as single agents.

Although there is no current clinical trial of targeted therapy for UTUC due to the rarity of the disease, numerous ongoing and developing clinical trials are testing the efficacy of targeted therapies for UCB in multiple molecular pathways, including antiangiogenic agents, anti-EGFR/HER2 therapy, anti-PI3K/AKT/mTOR therapy, and immune checkpoint inhibition [54**]. Genomic characterization before treatment is now being implemented in novel clinical trial designs in order to allocate patients based on predictive biomarkers for targeted molecular therapy [54]. MATCH-UP (Molecular Allocation Trial to CHoose therapy for metastatic Urothelial carcinoma following Platinum-based chemo-therapy) is a phase II trial designed to prospectively screen tumor tissues for specific molecular mutations, including *FGFR3* fusion/mutation/amplification, *RB1* mutation, PI3K mutation, *AKT1* mutation/amplification, mTOR mutation, *TSC1* deletion/mutation, *PTEN* deletion/mutation, *ERBB2* mutation/fusion/amplification, *EGFR* amplification, and histone acetyltransferase mutation[54].

Molecular characterization of tumor tissue may also predict an individual patient's likelihood of responding to a specific chemotherapy regimen. A novel gene expression algorithm Co-eXpression ExtrapolatioN (COXEN) is derived by comparing gene expression signatures between 60 cancer cell lines (NCI-60) that are sensitive or resistant to a number of FDA-approved drugs. A COXEN "score" using a gene expression model allows an prior

analysis of urothelial tumor responsiveness to anticancer agents and translate drug sensitivity of carcinoma cell lines into prediction of clinical response for a patient [55]. A Southwest Oncology Group clinical trial is currently recruiting patients to explore the role of COXEN score for predicting chemotherapy response in patients with urothelial cancer. Kothari et al. recently reported that COXEN accurately predicted drug sensitivity in 9/10 (90%) pts with response and 2/5 (40%) pts with resistance to therapy. The COXEN algorithm might have a role in urothelial cancer to select a “next best therapy” in the perioperative or metastatic setting [56].

Conclusions

UTUC is a highly heterogeneous disease with the majority of tumors harboring numerous concurrent genetic alterations. Currently, tumor stage and grade remain the best established predictors of prognosis in patients with UTUC. Recent molecular investigations of UTUC have led to an improved understanding of the genetic landscape, possible biomarkers, and identification of potentially actionable targets. In the near future, personalized genetic profiling of primary or metastatic UTUC tumors may become readily available for routine clinical decision-making. It is critical to explore, integrate and validate genetic data toward clinically meaningful outcomes for UTUC patients. The integration of molecular with clinical factors may improve our ability to determine prognosis, predict treatment response, and to select UTUC patients for targeted treatment options or clinical trials. More importantly, genetic data should be validated in future prospective multi-institutional studies and used in clinical practice for optimal decision-making toward the design of personalized therapies. Developing reliable prognostic biomarkers and promising drugs based on genomic alterations should translate into better clinical care and improved outcomes for UTUC patients.

Acknowledgments

This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748.

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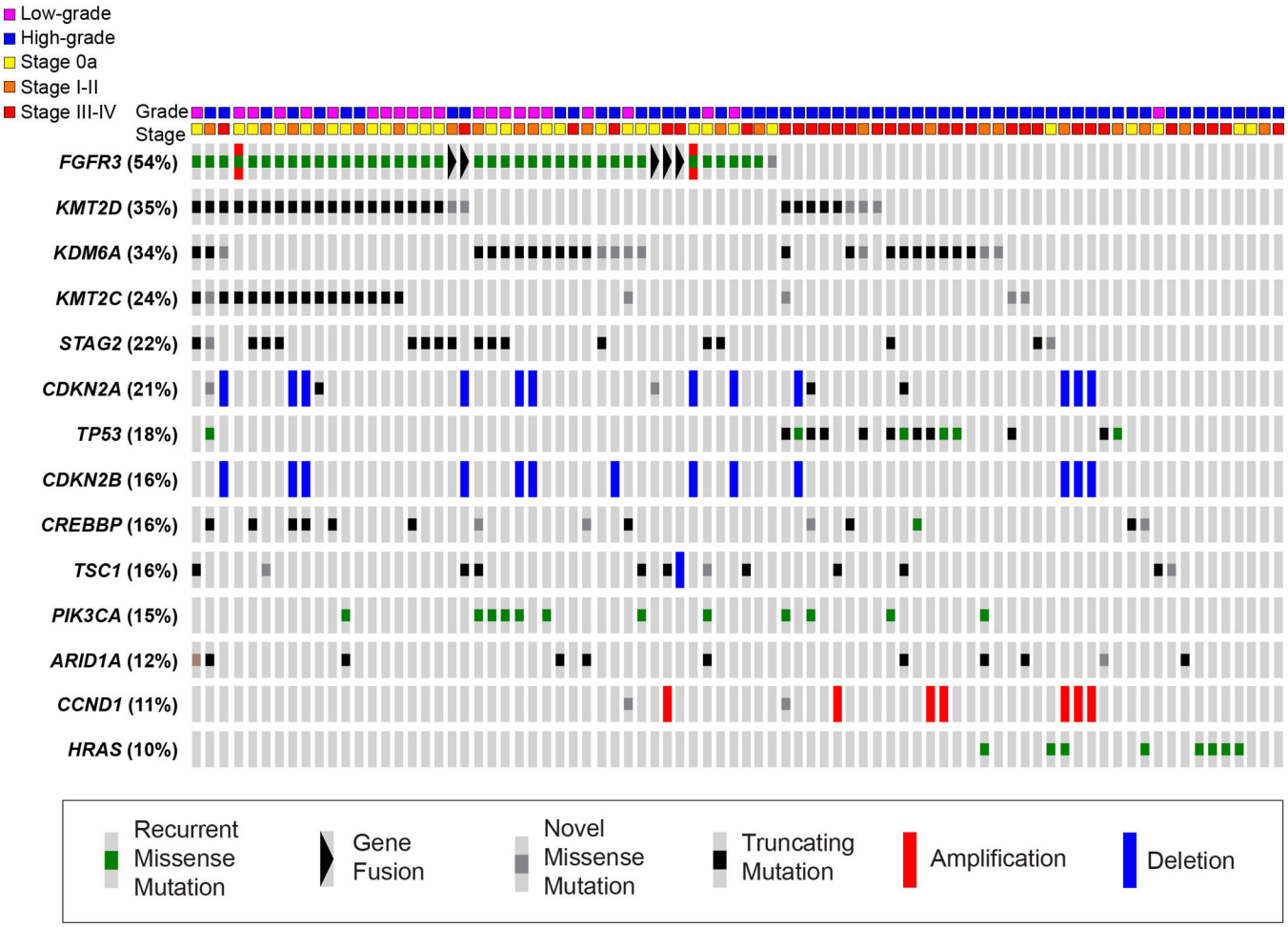

Figure 1.

Representation of the 14 most frequently altered genes in a series of 82 upper tract urothelial carcinoma tumors. Mutations are categorized as missense mutations reported in COSMIC (green), gene fusions (black triangle), novel missense mutations (gray), truncating nonsense mutations or indels (black), amplifications (red), and deletions (blue).

Table 1

Associations with genomic alterations and clinical outcomes in 82 patients with upper tract urothelial carcinoma treated with radical nephroureterectomy.

	Distant Recurrence (n=31 events)			Cancer-Specific Mortality (n=23 events)		
Gene	**HR (95% CI)**	**p***	**HG only p* (n=59)**	**HR (95% CI)**	**p***	**HG only p* (n=59)**
TP53/MDM2	3.66 (1.77, 7.57)	<0.001	0.048	3.43 (1.46, 8.08)	0.003	0.092
TP53	3.13 (1.44, 6.80)	0.002	0.114	3.25 (1.29, 8.21)	0.008	0.117
MDM2	2.64 (0.92, 7.59)	0.060	0.339	2.05 (0.61, 6.96)	0.239	0.619
Rb pathway	1.31 (0.64, 2.67)	0.458	0.908	1.20 (0.52, 2.77)	0.673	0.835
CCND1	5.19 (2.04, 13.22)	<0.001	0.011	3.50 (1.14, 10.72)	0.020	0.132
CCNE1	<NA>	<NA>	<NA>	<NA>	<NA>	<NA>
CDKN2A	1.20 (0.52, 2.79)	0.666	0.613	1.58 (0.62, 4.02)	0.334	0.193
CDKN2B	1.22 (0.50, 2.97)	0.667	0.438	1.69 (0.67, 4.30)	0.263	0.126
CDKN1A	0.41 (0.06, 3.03)	0.369	0.295	0.53 (0.07, 3.91)	0.523	0.490
E2F3	2.18 (0.30, 16.06)	0.434	0.747	<NA>	<NA>	<NA>
PI3K pathway	0.72 (0.31, 1.67)	0.442	0.892	0.58 (0.20, 1.72)	0.324	0.782
PIK3CA	0.32 (0.08, 1.34)	0.099	0.348	0.22 (0.03, 1.64)	0.105	0.300
PTEN	<NA>	<NA>	<NA>	<NA>	<NA>	<NA>
TSC1	1.12 (0.39, 3.22)	0.830	0.708	0.85 (0.20, 3.66)	0.828	0.930
TSC2	2.26 (0.53, 9.66)	0.259	0.156	1.83 (0.24, 14.08)	0.557	0.576
RTK/RAS/MAPK pathway	0.39 (0.19, 0.79)	0.006	0.301	0.48 (0.21, 1.09)	0.074	0.537
FGFR3	0.15 (0.06, 0.37)	<0.001	0.012	0.22 (0.08, 0.60)	0.001	0.116
ERBB2	2.77 (0.65, 11.80)	0.150	0.420	3.21 (0.74, 13.91)	0.099	0.292
ERBB3	3.93 (1.18, 13.10)	0.016	0.126	1.93 (0.25, 14.94)	0.524	0.786
HRAS	2.15 (0.75, 6.17)	0.144	0.595	2.10 (0.71, 6.19)	0.169	0.589
KRAS	1.32 (0.31, 5.53)	0.706	0.804	0.83 (0.11, 6.16)	0.854	0.553
BRAF	<NA>	<NA>	<NA>	<NA>	<NA>	<NA>
RAF1	0.90 (0.12, 6.60)	0.915	0.562	1.04 (0.14, 7.75)	0.971	0.710
NF1	0.48 (0.06, 3.49)	0.454	0.407	0.60 (0.08, 4.46)	0.614	0.622

	Distant Recurrence (n=31 events)			Cancer-Specific Mortality (n=23 events)		
Gene	**HR (95% CI)**	**p***	**HG only p* (n=59)**	**HR (95% CI)**	**p***	**HG only p* (n=59)**
Any Chromatin-Modifying Gene	0.69 (0.33, 1.44)	0.321	0.604	0.72 (0.31, 1.66)	0.433	0.569
ARID1A* or *SMARCA4	0.86 (0.35, 2.09)	0.731	0.801	0.55 (0.16, 1.86)	0.331	0.336
ARID1A	0.56 (0.17, 1.84)	0.333	0.292	<NA>	<NA>	<NA>
SMARCA4	1.35 (0.41, 4.47)	0.622	0.157	3.33 (0.90, 12.25)	0.055	0.021
CREBBP* or *EP300	0.37 (0.11, 1.22)	0.089	0.435	0.18 (0.02, 1.31)	0.055	0.235
CREBBP	0.35 (0.08, 1.46)	0.132	0.446	0.27 (0.04, 2.01)	0.170	0.469
EP300	0.37 (0.05, 2.69)	0.303	0.691	<NA>	<NA>	<NA>
KDM6A	0.76 (0.35, 1.65)	0.487	0.762	0.98 (0.40, 2.39)	0.965	0.829
***KMT2A* (*MLL*)**	5.09 (0.67, 38.72)	0.080	0.229	<NA>	<NA>	<NA>
***KMT2D* (*MLL2*)**	0.50 (0.21, 1.16)	0.098	0.316	0.59 (0.22, 1.59)	0.289	0.690
***KMT2C* (*MLL3*)**	0.29 (0.09, 0.94)	0.029	0.189	0.29 (0.07, 1.24)	0.075	0.255
STAG2	0.22 (0.05, 0.92)	0.022	0.221	0.35 (0.08, 1.51)	0.143	0.578

*p values reflect logrank test.

HR = hazard ratio; CI = confidence interval; HG = high-grade

Curr Urol Rep. Author manuscript; available in PMC 2016 April 07.