Immune Checkpoint Inhibitors in Advanced Upper and Lower Tract Urothelial Carcinoma: A Comparison of Outcomes

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ABSTRACT

Objectives

To compare clinical outcomes between patients with locally advanced (unresectable) or metastatic urothelial carcinoma (aUC) in the upper and lower urinary tract receiving immune checkpoint inhibitors (ICIs).

Patients and methods

We performed a retrospective cohort study collecting clinicopathologic, treatment, and outcome data for patients with aUC receiving ICIs from 2013 to 2020 across 24 institutions. We compared the objective response rate (ORR), overall survival (OS), and progression-free survival (PFS) between patients with upper and lower tract urothelial carcinoma (UTUC, LTUC). Univariable and multivariable logistic and Cox regression were used to assess the effect of UTUC on ORR, OS, and PFS. Subgroup analyses were performed stratified based on histology (pure, mixed) and line of treatment (first-line, subsequent-line).

Results

Out of a total of 746 eligible patients, 707, 717, and 738 were included in the ORR, OS, and PFS analyses, respectively. Our results did not contradict the hypothesis that patients with UTUC and LTUC had similar ORR (24% vs 28%, adjusted odds ratio [aOR]: 0.73, 95% confidence interval [CI]: 0.43-1.24), OS (median: 9.8 vs. 9.6

months, adjusted hazard ratio [aHR]: 0.93, 95% CI: 0.73-1.19), and PFS (median: 4.3 vs. 4.1 months, aHR: 1.01, 95% CI: 0.81-1.27). Patients with mixed-histology UTUC had significantly lower ORR and shorter PFS vs. mixed-histology LTUC (aOR: 0.20, 95% CI: 0.05-0.91 and aHR: 1.66, 95% CI: 1.06-2.59), respectively).

Conclusion

Overall, patients with UTUC and LTUC receiving ICIs have comparable response and outcomes. Subgroup analyses based on histology showed that those with mixed-histology UTUC had lower ORR and shorter PFS compared to mixed-histology LTUC. Further studies and evaluation of molecular biomarkers can help refine patient selection for immunotherapy.

Keywords: bladder cancer, checkpoint inhibitor, immunotherapy, upper tract urothelial cancer, variant histology

INTRODUCTION

Urothelial carcinoma is the 6th most common malignancy in the United States (US) and 5th most common malignancy in Europe. In 2020, bladder cancer is estimated to result in 17,980 deaths in the US and 49,185 deaths in Europe (1,2). About 90-95% of urothelial carcinomas (UCs) arise in the lower urinary tract (bladder and urethra), while the remaining 5-10% arise from the upper urinary tract (renal pelvis and ureter). Despite morphologic similarities, lower and upper tract urothelial carcinoma (LTUC, UTUC) have differences in epidemiology, tumor behavior, molecular characteristics, and prognosis (3–5). These differences may stem from distinct embryologic origins, anatomical location, genetic features, discordant staging, and practical considerations in diagnosis and management (6,7). Data regarding the management of UTUC are limited due to its lower prevalence. As a result, UTUC and LTUC are often treated as one entity with treatment decisions for UTUCs often informed based on data from LTUC-predominant populations, especially in the advanced disease setting. This approach may be suboptimal given the poorer outcomes for UTUC relative to LTUC with conventional LTUC-based therapies, when adjusted for stage (3).

The introduction of immune checkpoint inhibitors (ICIs) led to a paradigm shift in the treatment of locally advanced / unresectable or metastatic (a)UC for cisplatin-ineligible patients or after platinum-based chemotherapy (8). Five ICIs have been approved by the Food and Drug Administration (FDA) for treatment of aUC in the US, with pembrolizumab showing longer overall survival (OS) when compared to salvage chemotherapy (platinum-refractory setting) and avelumab plus best supportive care showing longer OS relative to best supportive care alone (post-platinum switch maintenance setting) (9,10). UTUC representation in ICI trials has been variable,

ranging from 14% to 30% (9–18). Data from subgroup analyses between UTUC and LTUC have been limited and conflicting, with a number of trials showing a higher objective response rate (ORR) in UTUC with atezolizumab (12), while others favored higher ORR in LTUC with pembrolizumab and avelumab (15,17). To address this knowledge gap, we compared ORR, progression free survival (PFS), and overall survival (OS) between patients with advanced UTUC and LTUC receiving ICIs, using a multi-institution retrospective cohort. We hypothesized that given similarities in the pathogenesis, treatment response and outcomes would be similar in advanced UTUC and LTUC.

PATIENTS AND METHODS

Patient Selection and Data Collection

After IRB approval, we performed a retrospective cohort study comparing oncologic outcomes between patients with UTUC and LTUC. Patients with pure- or mixed-histology aUC receiving ICI monotherapy for this indication were included. Those receiving ICIs as part of a clinical trial, in combination with another agent, for an indication other than aUC, or those who received multiple lines of ICIs were excluded. Patients with pure non-urothelial histology were also excluded. Each participating institution identified patients using provider driven and electronic health record search algorithms to allow for consecutive evaluation. The collected data included baseline characteristics (demographics, clinicopathological, and laboratory variables), treatment response, and long-term clinical outcomes. Data were collected by chart abstraction using secure, web-based, standardized REDCap electronic data capture tools hosted at the Institute of Translational Health Sciences (19). Data collected via alternative methods were uploaded into REDCap for secure storage and standardization of variables.

All patients underwent standard of care imaging as per treating provider. The evaluation of both best response and progression were determined according to the chart abstractor's assessment based on best available information from clinical notes and radiographic studies and did not include a blinded central radiology review. Similarly, pathology assessment was based on chart abstraction and did not include central pathology review. The ORR was calculated as the sum of patients with investigator-designated (complete or partial) response divided by the total number of patients with available data. OS was measured from the date of ICI initiation until the date of death; patients that were still alive were censored at the date of last follow-up visit. PFS was measured from the date of ICI initiation until the date of radiographic and/or clinical progression, or death; patients without progression or death were censored at the date of last follow-up visit.

Statistical Analysis

Baseline characteristics were summarized with descriptive statistics and compared with chi-square test and Student's t-test for categorical and continuous variables, respectively. Univariable and multivariable logistic regression was used to estimate the odds ratio (OR) and 95% confidence interval (CI) for ORR between UTUC and LTUC. In the multivariable analysis, we used two different a priori specified models based on the Bellmunt risk factors (20) – one adjusting for liver metastases, hemoglobin < 10 g/dL, and ECOG performance status > 0, individually; and the second model adjusting for the calculated Bellmunt score (i.e. liver metastases, hemoglobin < 10 g/dL, and ECOG performance status > 0).

We used the Kaplan-Meier method for survival curves and to estimate median (m)OS and median (m)PFS. Cox regression was used to determine the effect of tumor location on OS and PFS; differences between groups were expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). Similar to above, for the multivariable analysis, we used two different a priori specified models adjusting for individual Bellmunt risk factors (20) or for the calculated Bellmunt score.

Additional subgroup analyses were performed to compare outcomes between patients with LTUC and UTUC stratified by treatment line (first line and subsequent/salvage), histology (pure- and mixed-histology UC), and specific tumor location (renal pelvis, ureter, bladder, urethra) for all outcomes of interest. Statistical significance was set at $p < 0.05$; all p-values were two-tailed. All statistical analyses were performed using Stata IC 16.0 (StataCorp LLC, College Station, Texas).

RESULTS

Patient selection and characteristics

A total of 984 patients with aUC received ICIs monotherapy between 2013 and 2020 across 24 different institutions. After excluding ineligible patients, 746 patients were included in our population (**Figure 1**). A breakdown of patients according to institution is provided in **Supplemental Table 1**. Baseline patient characteristics are presented in **Table 1**. Men comprised 76% of patients with LTUC and 62% with UTUC; 71% had smoking history within LTUC and 59% within UTUC. Liver metastases were found in 18% of patients with LTUC and 29% of patients with UTUC. A breakdown of the mixed-histology UC variants for each group is provided in **Supplemental Table 2**.

Objective Response Rate

A total of 707 patients were included in the ORR evaluable population with 83% having LTUC and 17% UTUC. Our results did not contradict the hypothesis that patients with UTUC and LTUC had similar ORR (24% vs 28%, OR: 0.81, 95% CI: 0.52-1.27, p = 0.36; **Table 2**). Similarly, this hypothesis was not contradicted in either

of the two multivariable logistic regression models or when further stratifying for either specific tumor location (not shown) or treatment line.

In the subgroup analysis according to histology, patients with mixed-histology UTUC (n = 28) had significantly lower ORR compared to those with mixed-histology LTUC (n = 170) (11% vs 29%; model 1: adjusted (a)OR: 0.20, 95% CI: 0.05-0.91, p = 0.03 / model 2: aOR: 0.28, 95% CI: 0.08-0.98, p = 0.047).

Overall Survival

A total of 717 patients were included in the OS analysis with 82% having LTUC and 18% UTUC. Our results did not contradict the hypothesis that patients with UTUC and LTUC had similar OS (mOS: 9.8 months, 95% CI: 7.9-14.3 months vs. 9.6 months, 95% CI: 8.2-11.4 months; HR: 0.97, 95% CI: 0.76-1.25, p = 0.84; **Figure 2A, Table 3**). This remained true following adjustment in multivariable models (model 1: adjusted (a)HR: 0.92, 95% CI: 0.69-1.21, p = 0.53 / model 2: aHR: 0.93, 95% CI: 0.73-1.19, p = 0.58) or after stratifying by specific tumor location (not shown), line of therapy, or histology.

Progression-Free Survival

A total of 738 patients were included in the PFS analysis with 83% and 17% with LTUC and UTUC, respectively. The mPFS was 4.1 months (95% CI: 3.5-4.9 months) in the LTUC group and 4.3 months (95% CI: 3.2-5.9 months) in the UTUC group **(Figure 2B, Table 4)**. Our results did not contradict the hypothesis that patients with UTUC and LTUC had similar PFS with univariable (HR: 1.05, 95% CI: 0.84-1.32, p = 0.65) and multivariable Cox regression, or after stratifying by specific tumor location (not shown) or line of therapy.

In the subgroup analysis according to histology, patients with mixed-histology LTUC (n = 178) had mPFS of 4.3 months (95% CI: 3.0-7.4 months), compared to 2.2 months (95% CI: 1.6-5.9 months) in patients with mixed-histology UTUC (n = 30); mixed-histology UTUC was associated with shorter PFS in the multivariable Cox regression adjusting for the calculated Bellmunt score (aHR: 1.66, 95% CI: 1.06-2.59, p = 0.03).

DISCUSSION

In this multicenter retrospective cohort study of patients with aUC receiving ICIs, our data did not contradict the null hypothesis that ORR, OS, and PFS were similar between patients with UTUC and LTUC. However, patients with mixed-histology UTUC had lower ORR and shorter PFS compared to patients with mixed-histology LTUC.

Previous clinical trials investigating the safety and efficacy of ICIs in aUC have provided conflicting data about the outcomes of ICI treatment for patients with advanced UTUC. In the cisplatin-ineligible cohort of the

IMvigor210 phase II trial on atezolizumab, the ORR was numerically higher in UTUC (39%, 13/33) compared to LTUC (16%, 14/85) (12). In contrast, the ORR of UTUC was numerically lower compared to LTUC in the platinum-refractory cohort of the IMVigor210 trial (UTUC: 13%, 7/52 vs. LTUC: 23%, 39/168) (21), the IMvigor211 phase III trial on atezolizumab (UTUC: 11%, 10/94 vs. LTUC: 18%, 44/245) (21), the KEYNOTE-052 phase II trial of pembrolizumab (UTUC: 22%, 13/59 vs. LTUC: 28%, 70/247) (15), and the JAVELIN phase I trial of avelumab (UTUC: 11%, 4/36 vs. LTUC: 18%, 23/125) (17). In regards to OS, UTUC and LTUC had comparable mOS according to an updated analysis of the platinum-refractory cohort of the IMvigor210 trial (UTUC: 7.9 months vs. LTUC: 7.6 months) (25) and a post-hoc analysis of the IMvigor211 trial (UTUC: 10.9 months vs. LTUC: 9.7 months) (19). The exploratory subset analysis of the KEYNOTE 045 phase III trial suggested that pembrolizumab prolonged OS in both UTUC (HR: 0.53, 95% CI: 0.28-1.01) and LTUC (HR: 0.77, 95% CI: 0.60-0.97) compared to chemotherapy (9). In our study, the ORR, OS, and PFS were similar between the two groups. The exact tumor location in the urinary tract did not influence the results, although previous reports have shown differences in genomic features between renal pelvis and ureteral tumors (22).

In our cohort, patients with mixed-histology UTUC histology had significantly lower ORR (11%) compared to those with mixed-histology LTUC (29%). The breakdown of the mixed-histology UC variants among the two subgroups was largely similar. Prior prospective and retrospective studies have not suggested worse outcomes with ICI treatment for those with variant histology. In a recent phase II trial of dual immune checkpoint blockade with nivolumab/ipilimumab in rare genitourinary malignancies, the ORR among the 19 patients with variant histology bladder cancer was 37% (23). Further, a previous retrospective analysis using a smaller size cohort in our multicenter database only noted neuroendocrine histology to be associated with worse outcomes with ICI therapy, while other variants showed no significant differences (24). In our current study, patients with mixed-histology UTUC had significantly lower ORR than mixed-histology LTUC after adjusting for Bellmunt score. Therefore, we hypothesize that this difference may be attributed to inherent biologic differences rather than confounding prognostic factors; however, this hypothesis needs to be further tested. Notably, previous studies have reported significant differences in the genomic makeup, transcriptomic profile, and immunogenicity context between UTUC and LTUC (4,5,25), and among the different mixed-histology UC variants (26). This may suggest that patients with variant histology in UTUC are a particularly high-risk population.

There are several potential underlying mechanisms behind the differences in the response to ICIs among individuals. As with many solid tumors, the degree of T-cell infiltration in the tumor microenvironment has prognostic value in aUC (27). Specifically, the non-T-cell-inflamed tumor phenotype has been associated with poor response to ICI and worse prognosis (28). Most patients with UTUC express the non-T-cell-inflamed

phenotype, which may account for the lower ORR and inferior survival of patients with UTUC in a number of clinical trials (15,17,21,25). Molecular pathways associated with the non-T-cell-inflamed phenotype include the β-catenin, PPAR-γ, and FGFR3-driven pathways (29). Many UTUC tumors may have FGFR3 mutation or fusion (up to 40-60% in high-grade, up to 74% low-grade), significantly higher compared to LTUC, which may be associated with the non-T-cell-inflamed phenotype (22,25,30,31). However, the prognostic and predictive (regarding benefit with ICI) value of FGFR3 activating mutation or fusion is still uncertain (32,33). On the other hand, UTUC is associated with an only slightly higher rate of microsatellite instability (MSI) compared to LTUC (22,34). Tumors with MSI seem to have better response to ICI (12,35). Epigenetic factors may also account for differences in response to ICI (6).

Despite the demonstrated activity of ICIs in the platinum-refractory space, patients receiving ICIs for aUC still have a poor prognosis. As with previous clinical trials, the ORR to ICI therapy in our study was below 30% regardless of tumor location. In addition, the mPFS and mOS did not exceed 5 and 10 months, respectively, implying that most patients have progression in a short amount of time and die from the disease a few months later. Therefore, more work is needed to identify biomarkers, new therapy targets, and other strategies to guide therapy selection and optimize outcomes. While clinical models to predict response or survival have been proposed (36,37), much work remains to identify and prospectively validate predictive tools. Newer techniques, such as "liquid biopsy" may also provide a minimally invasive alternative to conventional tumor tissue analysis for next generation sequencing (38–41). In addition, there are strategies aiming to improve the efficacy of ICIs in aUC by combining them with i) other ICIs, ii) anti-FGFR3 targeted agents, iii) platinum-based chemotherapy, iv) localized treatments (e.g., radiotherapy), and v) antibody-drug conjugates (e.g. enfortumab vedotin, sacituzumab govitecan), among others (42–44). As with many combination regimens, we should carefully consider whether potential improvement of outcomes is the result of drug independence (which may address tumor heterogeneity among patients) rather than true additivity or synergism (which may address intra-tumor heterogeneity in an individual patient) (45).

The strengths of our study include a large sample size and diverse patient population originating from multiple institutions across North America and Europe, approaching in a "real world" setting. Nonetheless, limitations still apply and warrant careful interpretation of our results. Our study was retrospective in nature and lacked patient randomization, matching, or other adjustments to fully address potential confounding or selection biases. ECOG performance status, which may affect survival with ICI therapy in aUC (46), was missing in a proportion of patients. We were unable to examine differences in T-cell infiltration/density, biomarker expression (e.g., PD-L1, gene expression profiling, DNA damage response gene mutations, MSI status, tumor mutational burden), across different subgroups, which may be related to ICI response (25,47). There could have been

heterogeneity in data collection and treatment (and surveillance) practices across participating institutions. For example, imaging to assess progression was performed based on routine care rather than standardized time intervals. In addition, there was no central radiology review to provide standardization. In particular, treatment response was assessed according to investigator evaluation instead of central review, which may account for the slightly higher ORR observed in our study compared to clinical trials (15,17). The lack of central pathology review precluded us from obtaining important histopathological information, such as the percentage of variant histology among different specimens. Histopathological assessment was performed according to the standard practices of each participating institution; however, all the institutions have focused pathology expertise in urothelial cancer as tertiary referral centers. These practices may have significantly varied among institutions, due to differences in the size, source, and quality of tumor specimens, the percentages of tumor content, urothelial, and variant tumor tissue, as well as inter-observer variability. Finally, we were unable to obtain granular data on the breakdown of locally advanced (unresectable) vs. metastatic disease in each group, response to previous therapy, and time interval from last dose of previous therapy to ICI initiation.

CONCLUSION

Clinical trial data on response and outcomes of ICIs in UTUC are conflicting. In our study, patients with UTUC and LTUC receiving ICIs were noted to have similar ORR, OS, and PFS. However, mixed-histology UTUC had significantly lower ORR and shorter PFS compared to mixed-histology LTUC. Further studies and evaluation of molecular biomarkers can help optimize patient selection for ICI therapy.

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FIGURE LEGENDS

Figure 1. Consolidated Standards of Reporting Trials diagram of patient selection. aUC: advanced urothelial carcinoma; ICI: immune checkpoint inhibitor; ORR: objective response rate; OS: overall survival; PFS: progression-free survival.

Figure 2. Kaplan-Meier curve of A) overall survival and B) progression-free survival according to tumor location. ICI: immune checkpoint inhibitor; UTUC: upper tract urothelial carcinoma; LTUC: lower tract urothelial carcinoma

Table 1. Baseline patient characteristics.

	UTUC	LTUC	p value
Number of patients	130	616	
Age, mean (SD)	70 (10)	69 (10)	0.39
Men	80 (62)	469 (76)	**< 0.001**
White Race	99 (76)	456 (74)	0.61
Smoking history	77 (59)	434 (71)	**0.01**
Previous cystectomy / (nephro)ureterectomy			
Yes	80 (62)	300 (52)	**0.05**
Missing information	N/A	39/616	
Prior platinum-based (cisplatin or carboplatin) chemotherapy	80 (62)	406 (66)	0.34
Site of primary tumor			
Bladder	N/A	610 (99)	
Urethra	N/A	6 (1)	
Upper genitourinary system (unspecified)	45 (35)	N/A	
Renal pelvis	58 (45)	N/A	
Ureter	27 (21)	N/A	
Histology			
Pure urothelial	100 (77)	438 (71)	0.20
Mixed urothelial	30 (23)	176 (29)	
Hemoglobin < 10 g/dL	33 (27)	163 (27)	0.92
Liver metastasis	37 (29)	112 (18)	**0.01**
ECOG Performance Status			
0	26 (24)	120 (21)	0.86
1	58 (54)	304 (54)	
2	20 (19)	121 (22)	
3	4 (4)	16 (3)	
4	0 (0)	2 (1)	
Missing information	22/130	53/616	
Bellmunt risk factors			
0	20 (15)	90 (15)	0.27

1	57 (44)	310 (50)	
2	42 (32)	187 (30)	
3	11 (9)	29 (5)	
Type of ICI			
Atezolizumab	49 (38)	292 (48)	0.18
Pembrolizumab	67 (52)	252 (41)	
Nivolumab	9 (7)	44 (7)	
Durvalumab	3 (2)	17 (3)	
Avelumab	0 (0)	5 (1)	

Values are expressed as n (%) unless otherwise specified. UTUC: upper tract urothelial carcinoma; LTUC: lower tract urothelial carcinoma; ECOG: Eastern Cooperative Oncology Group; ICI: immune checkpoint inhibitor.

Table 2. Objective response rate according to tumor location.

Analysis	Location	ORR (%) (95% CI)	Univariable, OR (95% CI)	Multivariable 1, OR (95% CI)	Multivariable 2, OR (95% CI)
Primary	LTUC (n = 584)	28 (25-32)	Reference	Reference	Reference
	UTUC (n = 123)	24 (18-33)	0.81 (0.52-1.27)	0.73 (0.43-1.24)	0.83 (0.53-1.31)
Subgroup by histology	Pure LTUC (n = 414)	28 (24-33)	Reference	Reference	Reference
	Pure UTUC (n = 95)	28 (20-38)	1.02 (0.62-1.67)	1.00 (0.56-1.78)	1.06 (0.65-1.75)
	Mixed LTUC (n = 170)	29 (23-37)	Reference	Reference	Reference
	Mixed UTUC (n = 28)	11 (4-29)	0.29 (0.09-1.00)	0.20 (0.05-0.91)	0.28 (0.08-0.98)
Subgroup by line of therapy	First-line LTUC (n = 328)	31 (26-36)	Reference	Reference	Reference
	First-line UTUC (n = 57)	35 (24-48)	1.23 (0.68-2.23)	1.17 (0.58-2.37)	1.25 (0.69-2.28)
	Subsequent-line LTUC (n = 256)	26 (21-32)	Reference	Reference	Reference
	Subsequent-line UTUC (n = 66)	15 (8-26)	0.51 (0.25-1.06)	0.51 (0.22-1.20)	0.53 (0.25-1.09)

ORR: objective response rate; OR: odds ratio; CI: confidence interval; UTUC: upper tract urothelial carcinoma; LTUC: lower tract urothelial carcinoma

Table 3. Overall survival (OS) according to tumor location.

Analysis	Location	Median OS (95% CI) *	Univariable, HR (95% CI)	Multivariable 1, HR (95% CI)	Multivariable 2, HR (95% CI)
Primary	LTUC (n = 590)	9.6 (8.2-11.4)	Reference	Reference	Reference
	UTUC (n = 127)	9.8 (7.9-14.3)	0.97 (0.76-1.25)	0.92 (0.69-1.21)	0.93 (0.73-1.19)
Subgroup by histology	Pure LTUC (n = 417)	9.3 (7.8-11.4)	Reference	Reference	Reference
	Pure UTUC (n = 98)	10.9 (8.3-14.4)	0.89 (0.67-1.18)	0.78 (0.55-1.08)	0.83 (0.62-1.10)
	Mixed LTUC (n = 173)	10.6 (6.7-14.1)	Reference	Reference	Reference
	Mixed UTUC (n = 29)	7.6 (2.4-19.1)	1.30 (0.82-2.09)	1.46 (0.88-2.41)	1.36 (0.85-2.17)
Subgroup by line of therapy	First-line LTUC (n = 339)	10.9 (7.9-13.2)	Reference	Reference	Reference
	First-line UTUC (n = 62)	13.4 (8.3-19.9)	0.89 (0.62-1.29)	0.77 (0.50-1.19)	0.85 (0.58-1.24)
	Subsequent-line LTUC (n = 251)	8.6 (7.3-10.9)	Reference	Reference	Reference
	Subsequent-line UTUC (n = 65)	8.4 (5.3-14.0)	1.03 (0.74-1.43)	0.94 (0.65-1.36)	1.05 (0.75-1.46)

*in months; HR: hazard ratio; CI: confidence interval; UTUC: upper tract urothelial carcinoma; LTUC: lower tract urothelial carcinoma

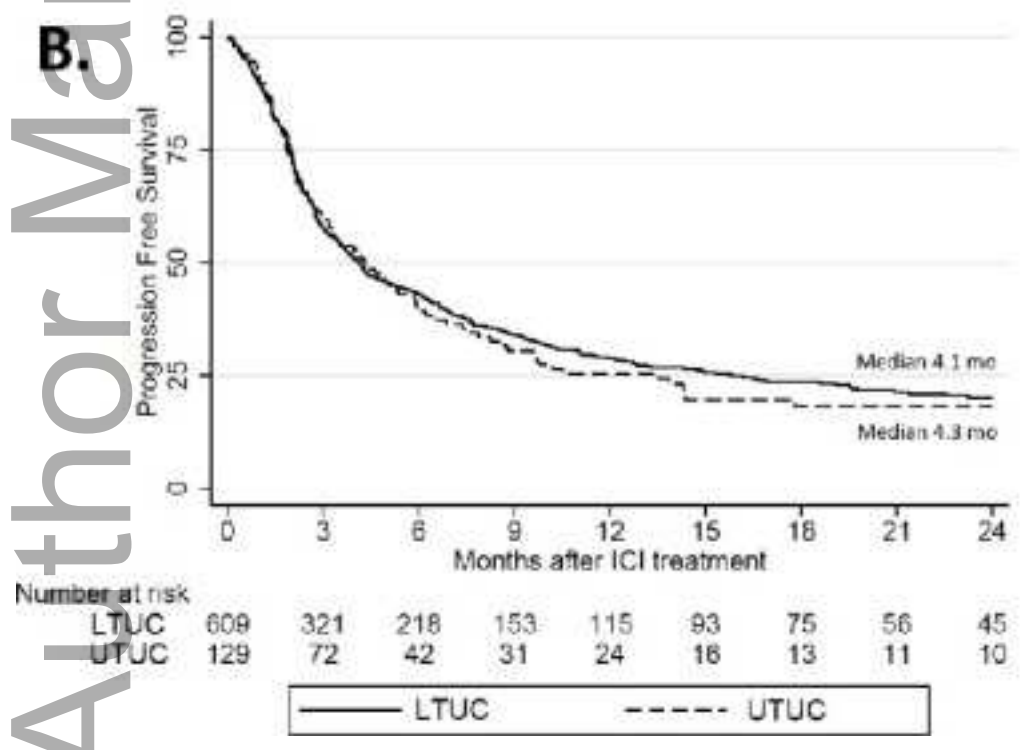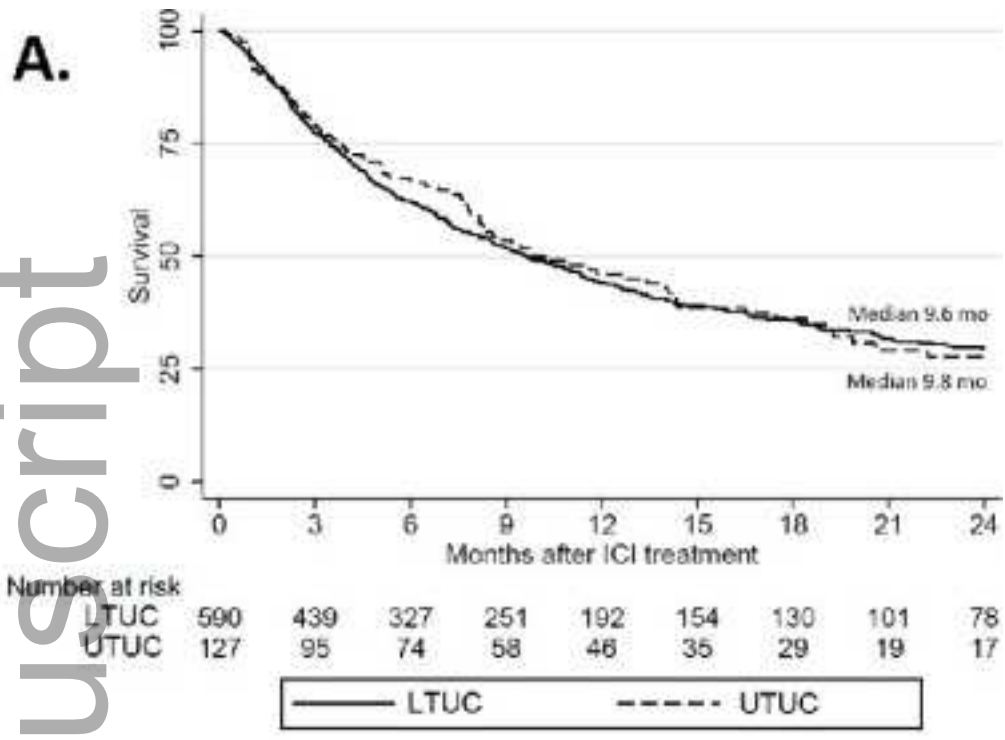**Table 4.** Progression-free survival (PFS) according to tumor location.

Analysis	Location	Median PFS (95% CI) *	Univariable, HR (95% CI)	Multivariable 1, HR (95% CI)	Multivariable 2, HR (95% CI)
Primary	LTUC (n = 609)	4.1 (3.5-4.9)	Reference	Reference	Reference
	UTUC (n = 129)	4.3 (3.2-5.9)	1.05 (0.84-1.32)	0.98 (0.76-1.26)	1.01 (0.81-1.27)
Subgroup by histology	Pure LTUC (n = 431)	4.1 (3.4-4.9)	Reference	Reference	Reference
	Pure UTUC (n = 99)	4.6 (3.3-6.9)	0.93 (0.72-1.21)	0.83 (0.61-1.12)	0.87 (0.67-1.13)
	Mixed LTUC (n = 178)	4.3 (3.0-7.4)	Reference	Reference	Reference
	Mixed UTUC (n = 30)	2.2 (1.6-5.9)	1.52 (0.98-2.37)	1.55 (0.97-2.49)	1.66 (1.06-2.59)
Subgroup by line of therapy	First-line LTUC (n = 347)	4.6 (3.5-6.3)	Reference	Reference	Reference
	First-line UTUC (n = 62)	4.6 (2.5-8.3)	1.04 (0.75-1.44)	0.85 (0.58-1.25)	1.01 (0.73-1.41)
	Subsequent-line LTUC (n = 262)	3.7 (3.0-4.4)	Reference	Reference	Reference
	Subsequent-line UTUC (n = 67)	4.1 (2.8-5.9)	1.04 (0.77-1.42)	0.98 (0.70-1.39)	1.07 (0.79-1.47)

*in months; HR: hazard ratio; CI: confidence interval; UTUC: upper tract urothelial carcinoma; LTUC: lower tract urothelial carcinoma

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A.

Number at risk

LTUC	590	439	327	251	192	154	130	101	78
UTUC	127	95	74	58	46	35	29	19	17

B.

Number at risk

LTUC	609	321	218	153	115	93	75	56	45
UTUC	129	72	42	31	24	16	13	11	10

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