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Original Article

Cancer-specific mortality in secondary bladder cancer after nephroureterectomy for upper tract urothelial carcinoma

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Abstract

Objective: To examine differences in cancer-specific mortality (CSM) in nonmetastatic upper tract urothelial carcinoma (UTUC) patients with vs. without secondary bladder cancer (BCa) after radical nephroureterectomy (RNU).

Methods: Within the Surveillance, Epidemiology, and End Results database (SEER 2000−2021), T1-T4N0M0 UTUC patients treated with RNU and diagnosed with secondary BCa were identified. A landmark approach was used, requiring the diagnosis of secondary BCa within 18 months of the UTUC diagnosis. Additionally, a minimum follow-up of 18 months after the UTUC diagnosis was required. Subsequently, Kaplan-Meier plots and time-dependent multivariable Cox regression (MCR) models were fitted. Sensitivity analyses were performed in patients with late BCa diagnoses (6 to 18 months after UTUC diagnosis).

Results: Of 3,013 eligible UTUC patients who fulfilled the landmark and follow-up criteria, 269 (9.0%) harbored secondary BCa. Ten-year CSM-free survival rates were respectively 60 vs 73% in patients with vs without secondary BCa. In MCR models, secondary BCa independently predicted higher CSM (hazard ratio [HR]: 1.53, $p < 0.001$). Subgroup analyses by tumor stage confirmed the independent

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predictor status of secondary BCa in T1−T2 stages (HR: 2.04, $p < 0.001$), primary renal pelvic (HR: 1.47, $p = 0.003$) and ureteral (HR: 1.63, $p = 0.01$) UTUC. Sensitivity analyses confirmed the independent predictor status of secondary BCa also in patients with late secondary BCa (HR: 1.68, $p < 0.001$).

Conclusion: In general, secondary BCa in UTUC patients treated with RNU is associated with higher CSM. This disadvantage primarily affects patients with T1−T2 stage UTUC involving the ureter or renal pelvis.

Keywords: CSM; UTUC; Secondary bladder; Radical nephroureterectomy; SEER

1. Introduction

Several reports have examined predictors of secondary bladder cancer (BCa) after radical nephroureterectomy (RNU) for upper tract urothelial carcinoma (UTUC) [1−5]. However, the literature on survival outcomes in UTUC patients with secondary BCa compared to those without secondary BCa after RNU remains limited and inconclusive. To the best of our knowledge, 3 single-institution [6−8] and 4 multi-institutional [9−12] retrospective studies have addressed the impact of secondary BCa on survival in UTUC patients following RNU. However, these studies were based on historical patient cohorts (diagnoses between 1983 and 2015), suffered from small sample sizes [6,9,10], or failed to addressed CSM [11]. Moreover, none of these studies focused on North American patients [6−12]. We addressed this knowledge gap and hypothesized that secondary BCa in UTUC patients is associated with higher CSM compared to those without secondary BCa. Additionally, we hypothesized that the impact of secondary BCa on CSM varies according to the stage of the primary UTUC (T1−T2 vs T3−T4) and/or tumor location (renal pelvis vs. ureter). To test these hypotheses, we relied on a large, contemporary (2000−2021) cohort of nonmetastatic UTUC patients treated with RNU from the SEER database, including those with and without secondary BCa.

2. Methods

2.1. Data source and study population

Within the SEER database (2000−2021), we selected patients aged ≥18 years with histologically confirmed urothelial carcinoma of the renal pelvis or ureter (ICD-10 site codes C65.9 and C66.9) as their first malignancy. In this cohort, we identified patients with urothelial bladder cancer (BCa) as a second malignancy, defined by ICD-O site codes C67.0−C67.9. Only patients with nonmetastatic UTUC treated with radical nephroureterectomy (RNU) and bladder cuff excision (BCE; surgery codes 40 and 70) were included. Patients who received perioperative chemotherapy, had unknown vital status, TX−T0 stage, NX-N1-3 stage, or those identified through autopsy or death certificates only, were excluded. Due to the anonymized nature of the SEER database, study-specific Institutional Review Board approval was waived.

2.2. Eligibility criteria and definition of variables for analyses

Landmark criteria required the diagnosis of secondary BCa within 18 months of the initial UTUC diagnosis. Eligible patients who fulfilled the landmark criteria were also required to benefit from at least 18 months of follow-up after initial UTUC diagnosis. The primary endpoint was urothelial cancer-specific mortality (CSM), defined as death resulting from urothelial carcinoma or either upper tract- or bladder urothelial carcinoma. Covariates included age at diagnosis (in years, continuously coded), sex (male vs female), tumor location (renal pelvis vs ureter), T stage (T1−T2 vs T3−T4), and tumor grade (low vs high), and lymph node dissection status (LND performed vs LND not performed).

2.3. Statistical analyses

First, baseline characteristics of cancer patients were tabulated. Descriptive statistics included frequencies and proportions for categorical variables, as well as medians and interquartile ranges (IQR) for continuous variables. Second, Kaplan-Meier (KM) depicted CSM-free survival rates according to presence or absence of secondary BCa. Third, time dependent multivariable Cox-regression (MCR) models addressing CSM were fitted. In all MCR models, adjusted for all the above reported covariates, the time dependent covariate represented the diagnosis of secondary BCa. Subsequent subgroup analyses were based on UTUC stage at presentation (T1−T2 vs T3−T4), as well as tumor location (ureteral vs. renal pelvic). Finally, to rule out possible synchronous disease, sensitivity analyses were performed only on patients with BCa diagnoses occurring between 6 and 18 months after the initial UTUC diagnosis. All tests were 2-sided, with a significance level of $P < 0.05$. The R software environment for statistical computing and graphics (R version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses [13].

Table 1
Descriptive characteristics of **3,013** eligible nonmetastatic urothelial upper tract cancer (UTUC) patients stratified according to presence or absence of secondary bladder cancer (BCa).

Characteristic	UTUC patients with secondary BCa *n* = 269 (9.0%)	UTUC patients without secondary BCa *n* = 2,744 (91.0%)	*P*-value[a]
Age at diagnosis, median (IQR)	69 (60, 76)	71 (63, 77)	0.03
Male Sex, n (%)	159 (59.1%)	1,541 (56.2%)	0.3
Tumor Location, n (%)			0.2
Renal Pelvis	192 (71.4%)	1,854 (67.6%)	
Ureter	77 (28.6%)	890 (32.4%)	
T stage, n (%)			0.5
T1–T2	184 (68.4%)	1,820 (66.3%)	
T3–T4	85 (31.6%)	924 (33.7%)	
Grade, n (%)			<0.001
Low grade	116 (43.1%)	834 (30.4%)	
High grade	153 (56.9%)	1,910 (69.6%)	
LND performed, n (%)	35 (13.0%)	608 (22.2%)	<0.001

[a] Wilcoxon rank sum test; Pearson's Chi-square test; Abbreviations: UTUC= upper tract urothelial cancinoma, BCa= bladder cancer, LND=lymphadenectomy.

3. Results

3.1. Descriptive characteristics of the study population

Overall, we identified 3,013 nonmetastatic UTUC patients treated with RNU who fulfilled the landmark as well as the follow-up criteria (Table 1). Of these, 269 (9.0%) harbored secondary BCa. Patients with secondary BCa were younger (median age 69 vs 71 years, $p = 0.03$) and more frequently harbored low-grade UTUC (43.1 vs 30.4%, $p < 0.001$). Additionally, patients with secondary BCa less frequently underwent RNU with LND (13.0 vs 22.2%, $p < 0.001$). No statistically significant differences were observed for tumor location ($p = 0.8$) , sex ($p = 0.3$), and UTUC stage ($p = 0.5$).

3.2. Effect of secondary BCa on cancer-specific mortality in the overall cohort

Ten-year CSM-free survival rates were 60 vs. 73% in respectively patients with vs. without secondary BCa (Fig. 1). In MCR models, presence of secondary BCa independently predicted higher CSM (hazard ratio [HR]: 1.53, confidence interval [CI]: 1.24–1.89; $p < 0.001$; Table 2). Sensitivity analyses confirmed secondary BCa as a

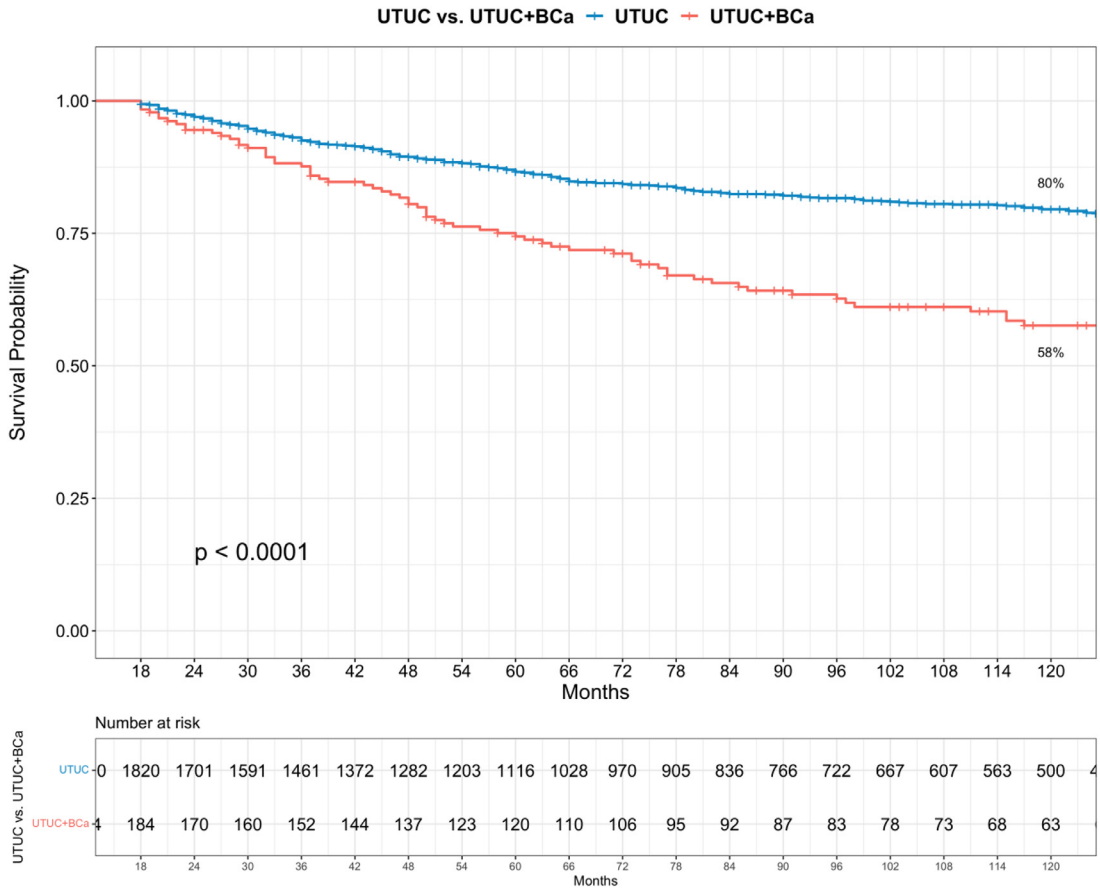

Fig. 1. Kaplan-Meier curve showing ten-year cancer-specific mortality-free survival in 3,013 eligible UTUC RNU-treated patients with vs without secondary BCa.

Table 2
Multivariable Cox regression models using the diagnosis of secondary BCa as a time-dependent covariate to predict cancer-specific mortality (CSM) in nonmetastatic urothelial upper tract cancer (UTUC) RNU-treated patients, analyzed in the overall cohort and by stage (T1−T2 vs T3−T4) and tumor location (renal pelvis vs ureteral) subgroups.

	HR	95% CI	*P*-value
Overall cohort[a]	1.53	1.24, 1.89	**<0.001**
Subgroups			
T1−T2 stages[b]	2.04	1.58, 2.64	**<0.001**
T3−T4 stages[b]	0.95	0.65, 1.38	0.7
Renal pelvic[c]	1.47	1.14, 1.89	**0.003**
Ureteral[c]	1.63	1.12, 2.38	**0.01**

HR = hazard ratio, CI = confidence interval.
[a] Adjusted for: age, sex, tumor location, stage, grade, LND status
[b] Adjusted for: age, sex, tumor location, grade, LND status
[c] Adjusted for: age, sex, stage, grade, LND status.

predictor of higher CSM in patients with a late diagnosis of BCa (HR: 1.68; CI 1.29, 2.18; $p < 0.001$).

3.3. Effect of secondary BCa on cancer-specific mortality in T1−T2 vs T3−T4 UTUC stages

In T1−T2 stages, of 2,004 eligible patients 184 (9.2%) harbored secondary BCa. Ten-year CSM-free survival rates were 58 vs. 80% in respectively patients with vs. without secondary BCa (Fig. 2). In MCR models, presence of secondary BCa independently predicted higher CSM (HR: 2.04, CI: 1.58−2.64; $p < 0.001$). Sensitivity analyses confirmed secondary BCa as a predictor of higher CSM in patients with a late diagnosis of BCa (HR: 2.17; CI 1.57, 3.01; $p < 0.001$).

In T3−T4 stages, of 1,009 eligible patients 85 (8.4%) harbored secondary BCa. Ten-year CSM-free survival rates were 64 vs. 61% in respectively patients with vs. without secondary BCa. In MCR models, no statistically significant differences in CSM were recorded in UTUC patients with vs. without secondary BCa. In sensitivity analyses no statistically significant differences in CSM were recorded in UTUC patients with vs. without late secondary BCa.

3.4. Effect of secondary BCa on cancer-specific mortality in renal pelvic vs ureteral UTUC

In renal pelvis patient subgroup, of 2,046 eligible patients 192 (9.3%) harbored secondary BCa. Ten-year CSM-free survival rates were respectively 61 vs. 74% in patients with vs. without secondary BCa (Figure 3). In MCR models, presence of secondary BCa independently predicted higher CSM (HR: 1.47, CI: 1.14−1.89; $p = 0.003$). Sensitivity analyses confirmed secondary BCa as a predictor of higher CSM in patients with a late diagnosis of BCa (HR: 1.61; CI 1.18, 2.20; $p = 0.002$).

In ureteral patient subgroup, of 967 eligible patients 77 (7.9%) harbored secondary BCa. Ten-year CSM-free survival rates were respectively 56 vs 72% in patients with vs. without secondary BCa. In MCR models, presence of secondary BCa independently predicted higher CSM (HR: 1.63, CI: 1.12−2.38; $p = 0.01$). Sensitivity analyses confirmed secondary BCa as a predictor of higher CSM in patients with a late diagnosis of BCa (HR: 1.76; CI 1.10, 2.8; $p = 0.01$).

4. Discussion

The association between secondary BCa and subsequent CSM in North American UTUC patients treated with RNU remains unknown. To address this knowledge gap, we used the SEER database (2000−2021) and tested whether secondary BCa is associated with CSM in nonmetastatic UTUC patients treated with RNU. We also examined whether this association varies based on primary UTUC stage (T1−T2 vs T3−T4) and/or tumor location (renal pelvis vs. ureter). We made several noteworthy observations.

First, we identified 3,013 nonmetastatic UTUC RNU treated patients with and without secondary BCa who fulfilled the landmark and follow-up requirements. This population is larger than that of all previous studies examining survival outcomes in UTUC patients with and without secondary BCa [9−12]. For example, in a historical (1995−2009) Japanese multi-institutional study conducted across 30 national centers, Kuroiwa et al. [11] identified 2,037 nonmetastatic RNU treated UTUC patients. Other historical single- and multi-institutional studies conducted outside North America [6−10,12] reported even fewer patients, ranging from 229 in the single-institutional report by Jiang et al. [8] to 760 in the multi-institutional study by Lee et al. conducted across five Korean centers [12]. In consequence, the current study is the largest to address nonmetastatic RNU treated UTUC patients with and without secondary BCa and the first to focus on a North American population. Moreover, these numbers suggest that very large-scale databases are required to study UTUC patients, and even larger databases are needed to specifically study nonmetastatic UTUC RNU treated patients with secondary BCa. In North America, besides multi-institutional studies, only 2 databases (SEER and National Cancer Database [NCDB]) provide sufficiently large sample sizes. Of those 2 the NCDB relies on the largest sample size [14−16]. However, within the NCDB discrimination between CSM vs. OCM is not made. This detail is crucial in analyses addressing nonmetastatic stages. In consequence, the SEER holds a critical advantage over NCDB and was used in the current analyses.

Second, within the current study, only 369 (9.0%) of the 3,013 eligible UTUC RNU treated patients harbored secondary BCa. This proportion is smaller than those reported in other single- and multi-institutional studies, where percentages ranged from 18.3% in the historical single-

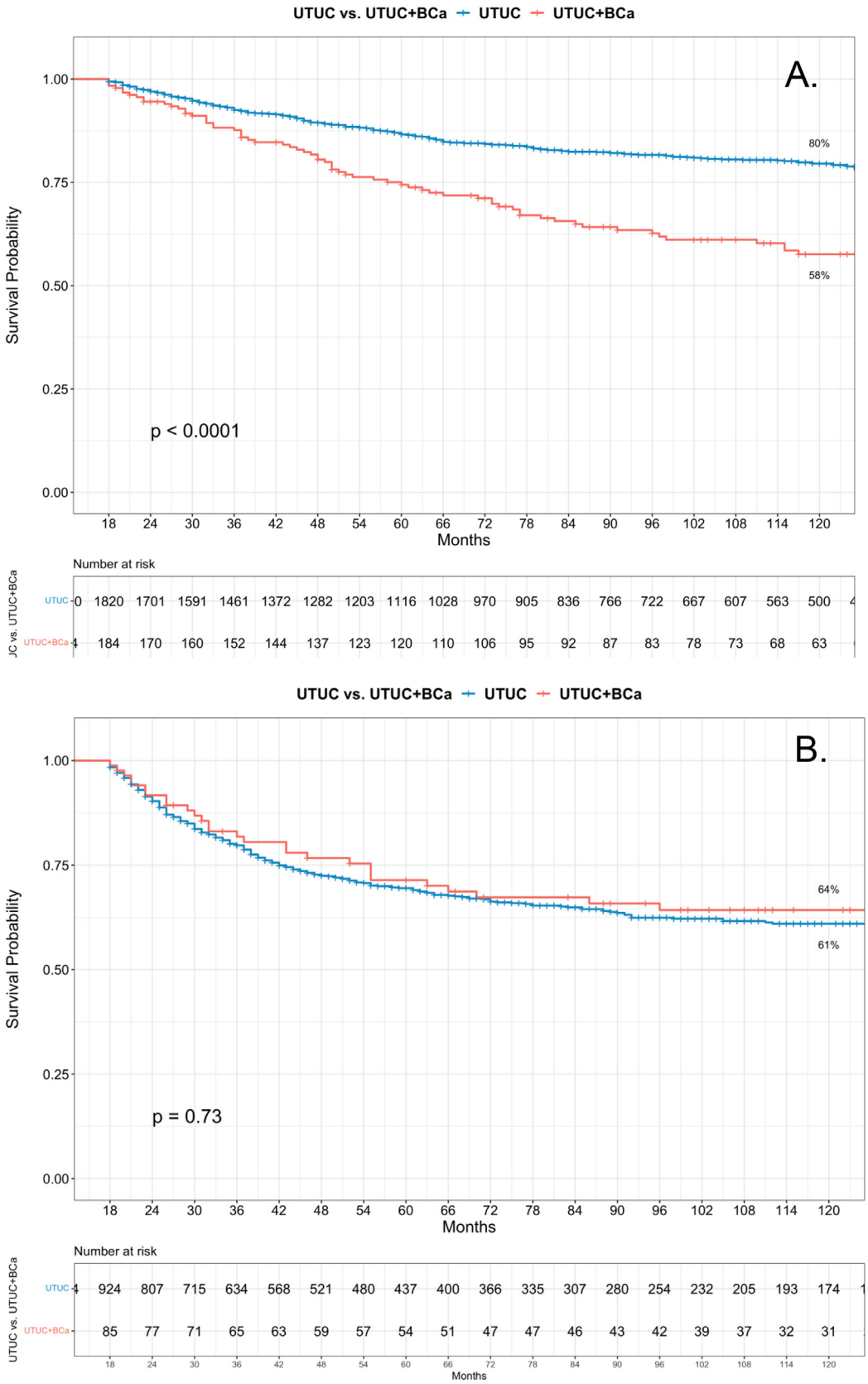

Fig. 2. Kaplan-Meier curve showing 10-year cancer-specific mortality-free survival in 2,004 T1−T2 (A) and in **1,009** T3−T4 (B) eligible UTUC RNU-treated patients with vs. without secondary BCa.

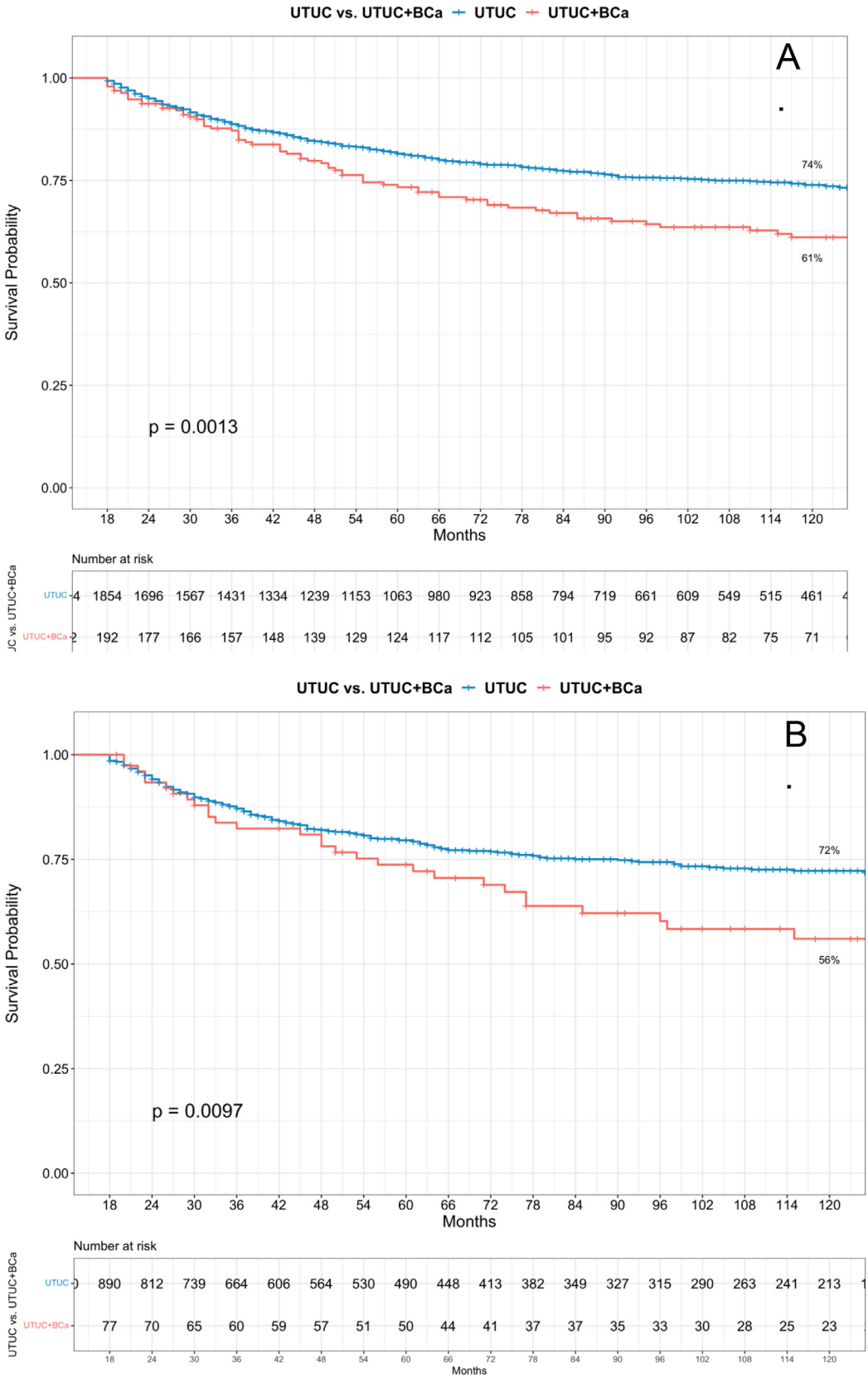

Fig. 3. Kaplan-Meier curve showing 10-year cancer-specific mortality-free survival in 2,046 renal pelvis (A) and in 967 ureteral (B) eligible UTUC RNU-treated patients with vs without secondary BCa.

institutional Chinese study by Jiang et al. [8] to 46.8% in the single-institution Egyptian study by Elawdy et al. [7]. Other studies from Japan, Korea, and France reported intermediate percentages that ranged from 27.8 to 38.4% [6,9–12]. These observations suggest possible differences in UTUC phenotypes based on the presence or absence of secondary BCa, which might be associated with the geographic location where UTUC patients are identified. Therefore, specific populations are needed to examine associations, as findings from Japanese, Chinese, French, or Egyptian studies may not be applicable to North American patients.

Third, we identified important differences in patient and tumor characteristics between UTUC patients with and without secondary BCa. Specifically, patients with secondary BCa were younger (median age 69 vs. 71 years) and more frequently harbored low-grade UTUC (43.1 vs. 30.4%). Additionally, patients with secondary BCa less frequently underwent LND and RNU (13.0 vs. 22.0%). These differences in patient and tumor characteristics highlight the necessity for multivariable adjustments when examining survival outcomes in patients with and without secondary BCa, as was done in the current study.

Fourth, we tested for differences in CSM in UTUC RNU treated patients with vs. without secondary BCa. To avoid immortal time bias, where analyses are biased by including patients diagnosed with secondary BCa many years after the initial UTUC diagnosis, we employed a landmark approach. This methodology considered only secondary BCa diagnoses made within the first 18 months after initial UTUC diagnosis for inclusion. Additionally, the current study required a minimum follow-up of 18 months after the initial UTUC diagnosis. Most previous studies addressing CSM in UTUC RNU-treated patients included secondary BCa diagnoses occurring beyond 18 months [6–8,10,12], and none of them required a minimum follow-up duration [6–12]. This choice may have not only artificially diminished the contribution of secondary BCa to potential CSM but also may have led to premature censoring, irreparably biasing the true association between secondary BCa and subsequent CSM. The current study incorporated all essential methodological steps within the eligibility criteria for inclusion.

Fifth, within the eligible patients who fulfilled both the landmark and follow-up criteria, ten-year CSM-free survival rates were 60% for patients with secondary BCa vs. 73% for those without secondary BCa. In time dependent MCR models, the presence of secondary BCa independently predicted higher CSM (HR: 1.53). Interestingly, this association was only validated in T1–T2 stages (HR: 2.04), but not in T3–T4 stages. These findings suggest that an aggressive initial UTUC phenotype (T3–T4 stages) results in very poor CSM. In consequence, CSM is unaffected by the presence or absence of secondary BCa. This hypothesis is consistent with the existing literature, where UTUC is known to behave more aggressively than urothelial carcinoma of the bladder [17,18]. Conversely, in localized UTUC patients with more favorable treated natural history, the subsequent diagnosis of secondary BCa significantly affects CSM. In these patients secondary BCa independently predicted higher CSM in both statistically significant and clinically meaningful fashion. Therefore, patients with T1–T2 UTUC treated with RNU require timely treatment and prevention strategies for secondary BCa. Several studies have investigated whether secondary BCa after RNU for UTUC affects oncological outcomes [6–12]. For example, Elalouf et al. [6] found that while bladder recurrence was not independently associated with worse cancer-specific survival (CSS), patients developing muscle-invasive bladder cancer (MIBC) after RNU experienced significantly poorer outcomes. Similarly, Yamashita et al. [10] showed that secondary BCa was an independent predictor of both CSS and overall survival in patients with nonmuscle invasive UTUC, underscoring the prognostic relevance of secondary BCa, especially when progression occurs. These findings support our observation that secondary bladder cancer following UTUC is not a benign event and may entail a worse prognosis compared to primary bladder cancer at similar stages, possibly due to delayed diagnosis, more aggressive tumor biology, or treatment-related factors.

Finally, we applied further stratification according to initial UTUC location: renal pelvic vs. ureteral. Presence of secondary BCa independently predicted higher CSM in both ureteral (HR: 1.63) and renal pelvic (HR: 1.47) location. These observations indicate that tumor location does not represent an effect modifier of the relationship between secondary BCa and subsequent CSM in primary UTUC. To the best of our knowledge, these observations are novel and are derived from a larger, more representative patient sample, examined with greater methodological rigor than prior studies.

Sixth, to assess the possible effect of synchronous BCa (BCa occurring concurrently with UTUC) on CSM, we performed sensitivity analyses in patients with late BCa diagnoses (6–18 months after UTUC diagnosis). In time-dependent multivariable models, BCa remained a predictor of higher CSM in the overall cohort of late secondary BCa (HR: 1.68) and in subgroups by T1–T2 stage (HR: 2.17), renal pelvic location (HR: 1.61), and ureteral location (HR: 1.76). These findings suggest that the impact of secondary BCa on survival in our original analyses is not solely due to early diagnoses that might represent synchronous disease but persists in later diagnoses, ruling out synchronous disease as a confounding factor.

Taken together, the current study provides novel and important insights into the effect of secondary BCa on CSM in nonmetastatic UTUC RNU treated patients. First, the current analysis has not previously been applied to North American patients and is based on a patient cohort larger than those in previous studies examining UTUC patients treated with RNU. Second, the current study

suggests that UTUC patients with secondary BCa exhibit differences in proportions by geographic location: 9.0% in the current study compared to 18.3% to 46.8% in studies conducted outside North America. Third, in the current study secondary BCa independently predicted higher CSM regardless of renal pelvic (HR: 1.47) vs. ureteral (HR: 1.63) location. Stage-specific subgroup analyses indicated that this association applies only to T1–T2 stages (HR: 2.05) and not to T3–T4 stages. Fourth, sensitivity analyses confirmed that secondary BCa remained a predictor of higher CSM even in patients with late BCa diagnoses, excluding bias from potential synchronous disease.

Despite its novelty, the present study is not devoid of limitations. First and foremost is its retrospective nature. This design type only allows testing for associations between secondary BCa and survival but does not allow for causal inference. Second, despite the large-scale of the SEER, the actual number of observations were relatively low. Unfortunately, larger databases that allow examination of the endpoints addressed in this study are not available. Third, while UTUC patients treated with RNU may benefit from additional therapies, such as systemic chemotherapy at metastatic progression or postoperative intravesical chemotherapy, these treatments are not fully captured in SEER. Finally, SEER lacks important clinical variables, including patient characteristics (e.g., performance status, comorbidities) and surgical details (e.g., surgical approach, surgeon experience, positive margins, extent of lymph node dissection, blood transfusions, and perioperative complications). However, all of the above limitations are shared with all other studies based on the SEER database or similar large-scale data repositories [19–21]. Additionally, these limitations apply equally to patients with and without secondary BCa and should not differentially impact the endpoint of interest.

5. Conclusion

In general, secondary BCa in UTUC patients treated with RNU is associated with higher CSM. This disadvantage primarily affects patients with T1–T2 stage UTUC involving the ureter or renal pelvis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Natali Rodriguez Peñaranda: Writing – review & editing, Writing – original draft, Software, Formal analysis, Conceptualization. **Francesco Di Bello:** Formal analysis. **Andrea Marmiroli:** Formal analysis. **Fabian Falkenbach:** Formal analysis. **Mattia Longoni:** Writing – original draft. **Quynh Chi Le:** Writing – original draft. **Calogero Catanzaro:** Writing – original draft. **Michele Nicolazzini:** Writing – original draft. **Mario de Angelis:** Conceptualization. **Jordan A. Goyal:** Data curation. **Fred Saad:** Writing – review & editing. **Shahrokh F. Shariat:** Supervision. **Gennaro Musi:** Supervision. **Markus Graefen:** Supervision. **Alberto Briganti:** Supervision. **Felix K.H. Chun:** Supervision. **Riccardo Schiavina:** Supervision. **Carlotta Palumbo:** Data curation. **Marco Ticonosco:** Data curation. **Stefano Resca:** Software. **Stefano Puliatti:** Writing – review & editing. **Salvatore Micali:** Writing – review & editing. **Pierre I. Karakiewicz:** Writing – review & editing, Writing – original draft, Conceptualization.

Availability of data

These data were derived from the Surveillance, Epidemiology, and End Results (SEER) database in the public domain: https://seer.cancer.gov/.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2025.08.006.

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