Are there differences between de novo and secondary upper tract urothelial carcinoma tumors?

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Abstract

Introduction: Upper tract urothelial carcinoma (UTUC) accounts for <5% of all urothelial cancers. We aimed to ascertain the clinical differences between UTUC tumous presenting de novo (DnUTUC) and those presenting secondary (SUTUC) following a bladder cancer diagnosis.

Methods: Our institutional database was queried for all UTUC patients who were surgically treated with radical nephroureterectomy or ureterectomy between 2003 and 2017. Bladder recurrence and cancer-specific mortality were compared. To reduce the possible bias due to confounding variables obtained from a simple comparison of outcomes, DnUTUC patients were matched (for age, gender, tumor location, type of surgery, grade, TNM staging, presence of carcinoma in situ, and lymphovascular invasion) with propensity score to SUTUC patients. Bladder recurrence and cancer-specific mortality were assessed with Cox proportional hazards model.

Results: A total of 117 UTUC patients were identified: 80 with DnUTUC (68.4%) and 37 with SUTUC (31.6%). A greater proportion of males with SUTUC was demonstrated (89.2% vs. 68.8; p=0.02). In both groups, 67.5% of patients had high-grade disease but SUTUC demonstrated a higher carcinoma in situ rate (43.2% vs. 25%; p=0.047). Univariate analysis demonstrated that the five-year bladder recurrence rate was trending to be higher in SUTUC (65.3% vs. 20.5%; p=0.099). In the Cox model, however, it was associated with increased bladder recurrence (hazard ratio [HR] 3.69; 95% confidence interval [CI] 1.68–8.09; p=0.001). Although univariate analysis demonstrated that SUTUC patients were more likely to die of their disease (30.6% vs. 9%; p=0.009), the multivariable Cox model did not demonstrate this association. The limitations of this study include its retrospective, single-center design and relatively small cohort of patients.

Conclusions: In this hypothesis-generating study, some evidence suggests that further research is needed to delineate differences between SUTUC and DnUTUC.

Introduction

Urothelial carcinomas, which may occur anywhere along the urothelial epithelium from the lower (urethra and bladder) to the upper (ureter, renal pelvis, and calyces) urinary tract, together are categorized as the fifth most common tumor site.[1] Upper tract urothelial cancer (UTUC), occurring in the ureter, renal pelvis, or calyces, accounts for 5–10% of all urothelial carcinoma.[2] These tumors are most common in people in their seventh decade and are more common in men.[3] Although also arising from urothelium, UTUC is increasingly being recognized as a different disease entity from bladder urothelial carcinoma. Firstly, although still controversial, evidence exists that bladder carcinoma occurs 3–4 times more commonly in men[4] compared to the ratio of 2:1 for men in UTUC.[3,5] Secondly, it has inferior survival in women, while this is not observed in UTUC.[6] Thirdly, at initial diagnosis, UTUC are more invasive tumors than bladder carcinoma (60% vs. 15–25%).[7,8] Lastly, recurrence in the form of UTUC is less likely to develop after bladder carcinoma (2–6%)[9] than for bladder carcinoma to develop after UTUC (22–47%).[10] Despite these clear differences, the underlying pathophysiology and management of UTUC have traditionally been extrapolated from our understanding and management of bladder carcinoma.[11] However, there is increasing evidence to suggest that UTUC has unique epidemiological, histological, molecular, and prognostic factors compared to bladder carcinoma.[12]

This led us to hypothesize that primary de novo UTUC (DnUTUC) is a distinct entity from secondary UTUC (SUTUC), which develops after a bladder carcinoma diagnosis and might me more closely associated with it. To date, no series has stratified UTUC in this manner and studied the differences, if any, between DnUTUC and SUTUC.

Methods

Patient cohort

After receiving approval by the institutional ethics committee, we performed a retrospective chart review of all patients older than 18 who underwent radical definitive surgery (nephroureterectomy or distal ureterectomy) for UTUC between 2003 and 2017 from the Princess Margaret Cancer Center institutional database. We excluded all patients who presented with metastatic disease. Additionally, due to the inclusion criteria, UTUC patients who underwent conservative or endoscopic management were also excluded. Conservative management of UTUC does not commonly occur in our facility and this type of treatment is usually undertaken at another facility. The purpose of these exclusions was to compare outcomes of UTUC patients with localized disease who were treated with a definitive radical treatment.

Surgical procedure and followup protocol

All nephroureterectomies were performed with excision of the entire ipsilateral ureter with a formal extravesical bladder cuff removal. All ureterectomy procedures were open procedures, while all nephroureterectomies were either open or laparoscopic combined with either a small open midline infra-umbilical or Gibson incision for removal of the distal ureter and bladder cuff. None of the patients in this cohort received postoperative intravesical instillation of mitomycin. Patients were stratified into two groups: those with DnUTUC and those with SUTUC.

Following surgery, patients who underwent either nephroureterectomy or ureterectomy were seen in the clinic every three months for the first year, every six months from the second to the fifth year, and annually thereafter. In each clinic visit, tests performed included a complete history, physical examination, blood tests (including complete blood count, and serum chemistry), urine cytology, cystoscopic examination of the bladder, and radiographic evaluation of the contralateral upper urinary tract either by computed tomography (CT) scan or ultrasound. Bladder recurrences were defined as definitive cystoscopic evidence of a tumor. Cause of death was defined by chart review or by death certificates.

Covariates and outcomes

We collected data on relevant demographic and tumor data, including patient age, gender, age-adjusted Charlson comorbidity score, smoking history, history of bladder carcinoma, tumor laterality and location, type of surgery (nephroureterectomy or distal ureterectomy, open vs. laparoscopic), pathologic grade, TNM staging, presence of carcinoma in situ (CIS) and lymphovascular invasion, and receipt of neoadjuvant and adjuvant chemotherapy. Outcomes data collected included bladder recurrence, followup duration, cancer-specific mortality (CSM), and last known clinical status. Importantly, bladder recurrence was defined as development of bladder carcinoma postoperatively, at a time where the patient was considered to be with no evidence of disease.

Statistical analysis

Descriptive analyses (mean with standard deviation and median with interquartile range [IQR]) was used for continuous variables and proportions for discrete variables; comparative tests included Chi-square for discrete variables and Kruskal-Wallis for continuous variables. Kaplan-Meier (KM) graphs (log-rank test) was used to evaluate recurrencefree survival (RFS), and cancer-specific survival (CSS), stratified according to whether UTUC was de novo or following a diagnosis of bladder carcinoma, and stratified according to the UTUC tumor location (renal pelvis or ureter). To reduce the possible bias due to confounding variables obtained from a simple comparison of outcomes, propensity score matching was performed. This was done (2:1 ratio) by age, gender, tumor location, type of surgery, tumor grade, TNM staging, presence of CIS, and lymphovascular invasion. Cox proportional hazards regression model was performed to identify factors predicting bladder recurrence and CSM. A priori covariates in the model included type of UTUC (DnUTUC or SUTUC) and the calculated propensity score. Statistical tests were two-tailed and a p-value <0.05 was considered statistically significant. All analyses were conducted using SPSS software version 23.0 (SPSS Inc., Chicago, IL, U.S.) and SAS 9.4 (SAS Institute, Cary, NC, U.S).

Results

A total of 122 patients with UTUC who were treated with either nephroureterectomy or ureterectomy were identified over this time. Only three patients were treated conservatively in an endoscopic manner and were referred to another center. Out of the 122 patients, five presented with metastatic disease and thus were excluded, leaving 117 patients with DnUTUC (80, 68.4%) and SUTUC (37, 31.6%). While all patients were diagnosed with UC, one patient from the DnUTUC group had micropapillary features on his final

pathology (1.25%). Five DnUTUC patients (4.3%) were diagnosed with Lynch syndrome, an autosomal-dominant genetic syndrome, harboring a high risk of colon cancer, as well as other malignancies, including UTUC. Table 1 demonstrates patient clinical and operative data. No statistically significant differences were noted in the age, age-adjusted Charlson score, smoking history, tumor laterality, and type of surgery patients underwent in both groups. However, the proportion of males in the SUTUC group was significantly higher (89.2% vs. 68.8%; p=0.02). In both groups, approximately 2/3 of the tumors were in the renal pelvis (63.75% and 64.9% in the DnUTUC and SUTUC groups, respectively). SUTUC tumors developed after a mean time (standard deviation [SD]) of 44 months (44.97) from bladder tumor treatment. Roughly 2/3 of the patients underwent an open procedure (60% and 64.9% of DnUTUC and SUTUC, respectively). Five of the open cases began as laparoscopic cases that were eventually converted to an open procedure.

Table 2 demonstrates pathological and followup data. Most patients in both groups had high-grade disease (67.5% and 67.6% in DnUTUC and SUTUC, respectively), and T stage distribution were similar as well, with 47.5% of DnUTUC and 51.4% of SUTUC patients having pTa disease. Lymph node dissection was done in only a third of the patients in both groups (32.5% and 32.4%), and no difference could be seen in the pathological node stage. Lymphovascular invasion and positive ureteral margin rates were also similar among both groups. CIS, however, was significantly more common in the SUTUC group (43.2% vs. 25%; p=0.047). Receipt of neoadjuvant and adjuvant chemotherapy, although similar in both groups, was not very common, with 3.75% and 5.4% of DnUTUC and SUTUC patients, respectively, receiving neoadjuvant chemotherapy, and 12.5% and 8.1% of DnUTUC and SUTUC patients, respectively, receiving adjuvant chemotherapy.

Median followup was similar, with 32.5 months (IQR 11.4–61.4) in DnUTUC and 39.5 months (IQR 20.6–63.4) in SUTUC (p=0.22). A total of 10 (of 37, 27%) SUTUC patients had undergone radical cystectomy prior to the development of SUTUC. After excluding these patients, although not statistically significant, the five-year bladder recurrence rate was demonstrated to be higher in the SUTC group (65.3%

Table 1. Patient demographic and operative data

	De novo UTUC	Secondary UTUC	p
Number of patients, n (%)	80 (68.4%)	37 (31.6%)	
Mean age, n (SD)	69.1 (12)	69.2 (9.7)	0.995
Gender, n (%)			
Male	55 (68.8%)	33 (89.2%)	0.02
Women	25 (31.3%)	4 (10.8%)	
Mean age adjusted Charlson score (SD)	6.5 (2.7)	6.7 (2.1)	0.68
Smoking status, n (%)			
Never	26 (32.5%)	6 (16.2%)	0.283
Past	30 (37.5%)	15 (40.5%)	
Current	15 (18.8%)	10 (27%)	
Unknown	9 (11.3%)	6 (16.2%)	
Tumor laterality, n (%)			
Right	41 (51.2%)	20 (54.1%)	0.618
Left	37 (46.3%)	17 (45.9%)	
Bilateral	2 (2.5%)	0	
Tumor location n, (%)			
Renal pelvis	51 (63.75%)	24 (64.9%)	0.869
Ureter	29 (36.25%)	14 (35.1%)	
Mean time from TURBT surgery to UTUC surgery, months (SD)	–	44 (44.97)	–
Type of surgery, n (%)			
Nephroureterectomy	67 (83.8%)	30 (81.1%)	0.721
Distal ureterectomy	13 (16.3%)	7 (18.9%)	
Surgery modality, n (%)			
Open	48 (60%)	24 (64.9%)	0.58
Laparoscopic	32 (40%)	13 (35.1%)	

SD: standard deviation; TURBT: transurethral resection of bladder tumor; UTUC: upper tract urothelial carcinoma.

Table 2. Pathological and followup outcomes

	De novo UTUC	Secondary UTUC	p
Pathology grade, n (%)			
Low	26 (32.5%)	12 (32.4%)	0.994
High	54 (67.5%)	25 (67.6%)	
Pathological T stage, n (%)			
Ta	38 (47.5%)	19 (51.4%)	0.55
T1	5 (6.3%)	4 (10.8%)	
T2	8 (10%)	6 (16.2%)	
T3	26 (32.5%)	8 (21.6%)	
T4	2 (2.5%)	0	
Tis	1 (1.3%)	0	
Pathological N stage, n (%)			
N0	20 (25%)	8 (21.6%)	0.912
N1	2 (2.5%)	1 (2.7%)	
N2	4 (5%)	3 (8.1%)	
NX	54 (67.5%)	26 (67.6%)	
CIS present, n (%)	20 (25%)	16 (43.2%)	0.047
Lymphovascular invasion present, n (%)	14 (17.9%)	6 (16.2%)	0.867
Positive ureteral margins, %	10.1%	16.2%	0.348
Receipt of neoadjuvant chemotherapy, n (%)	3 (3.75%)	2 (5.4%)	0.691
Receipt of adjuvant chemotherapy, n (%)	10 (12.5%)	3 (8.1%)	0.51
Mean followup time, months (SD)	42.6 (38.3)	40.9 (26.7)	0.808
Mean time to recurrence, months (SD)	35.11 (37.76)	32.85 (34.9)	0.758
Status at last followup, n (%)			
Alive with no evidence of disease	58 (72.5%)	17 (45.9%)	0.009
Alive with disease	11 (13.75%)	8 (21.6%)	
Dead of disease	7 (8.75%)	11 (29.7%)	
Dead of other causes	4 (5%)	1 (2.8%)	

CIS: carcinoma in situ; SD: standard deviation; UTUC: upper tract urothelial carcinoma.

vs. 20.5%; p=0.099), as seen in the KM analysis (Fig. 1A). However, there was a statistical significant difference in bladder recurrence rates after stratifying by tumor location for DnUTUC-only tumors (Fig. 1B), demonstrating renal pelvis tumors to have a lower five-year recurrence rate of 12.2% vs. 34.5% (p=0.047). No such difference was noted for the SUTUC patients (Fig. 1C), with five-year bladder recurrence rate of 66.6% vs. 62.5% for renal pelvis and ureteral tumours, respectively (p=0.242).

Overall, 15/37 (40.5%) SUTUC patients underwent radical cystectomy (RC), 10 patients prior to the development of SUTUC and five patients following SUTUC diagnosis (18.5%). In contrast, only 2/80 DnUTUC patients (2.5%) developed bladder carcinoma and underwent RC following DnUTUC diagnosis.

Propensity score matching with a 2:1 ratio was performed and resulted in a total of 83 patients being matched (54 in the DnUTUC group and 29 in the SUTUC group) (Supplementary Table 1). Cox proportional hazards regression analysis using the propensity score and type of UTUC (DnUTUC or SUTUC) evaluated the predictors of bladder recurrence (after excluding SUTUC patients who underwent cystectomy prior to SUTUC development), as seen in Table 3. This model demonstrated that SUTUC compared to DnUTUC was strongly associated with increased bladder recurrence rate (hazard ratio [HR] 3.837; 95% confidence interval [CI] 1.689–8.091; p=0.001).

CSM was significantly worse in SUTUC patients, as shown in the KM curve in Fig. 2A (five-year CSM rate of 22% vs. 9%, log-rank p=0.011). However, for both groups, no difference was discerned between CSM in renal pelvic and ureteral tumors (10.2% vs. 7.1%, p=0.121, and 21% vs. 25%, p=0.714 for DnUTUC and SUTUC, respectively), as can be seen in Figs. 2B and 2C. However, the Cox proportional hazards model demonstrated that although SUTUC was associated with worse CSM, this was not statistically significant (HR 2.246; 95% CI 0.79–6.391) (Table 3). A total of 11 (30.6%) SUTUC patients compared to only seven (9%) DnUTUC patients died of urothelial carcinoma during the study followup period (p=0.009).

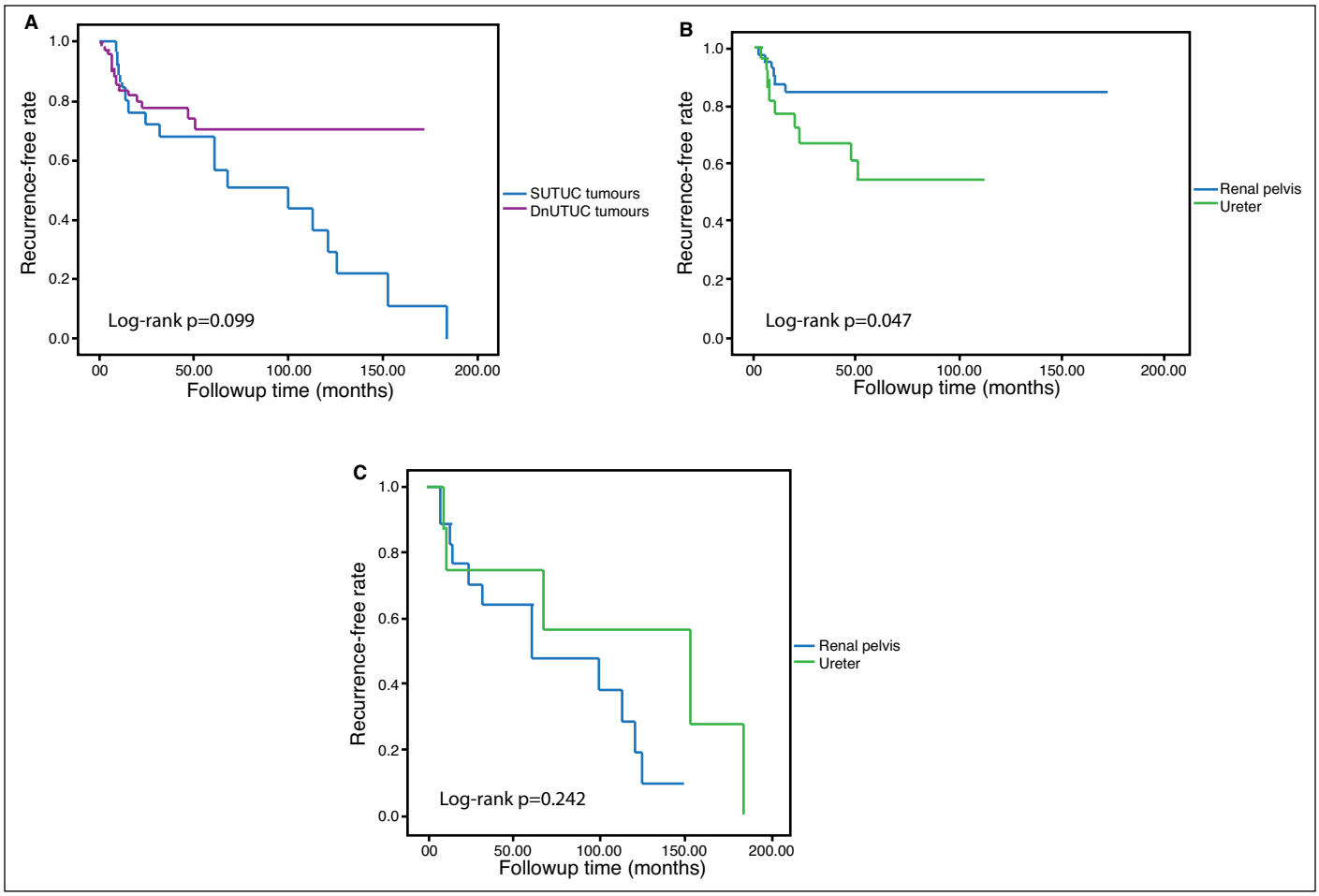

Fig. 1. Bladder recurrence-free survival in ***(A)*** all patients; ***(B)*** de novo upper tract urothelial carcinoma (UTUC) patients stratified by tumor location; and ***(C)*** secondary UTUC patients stratified by tumor location.

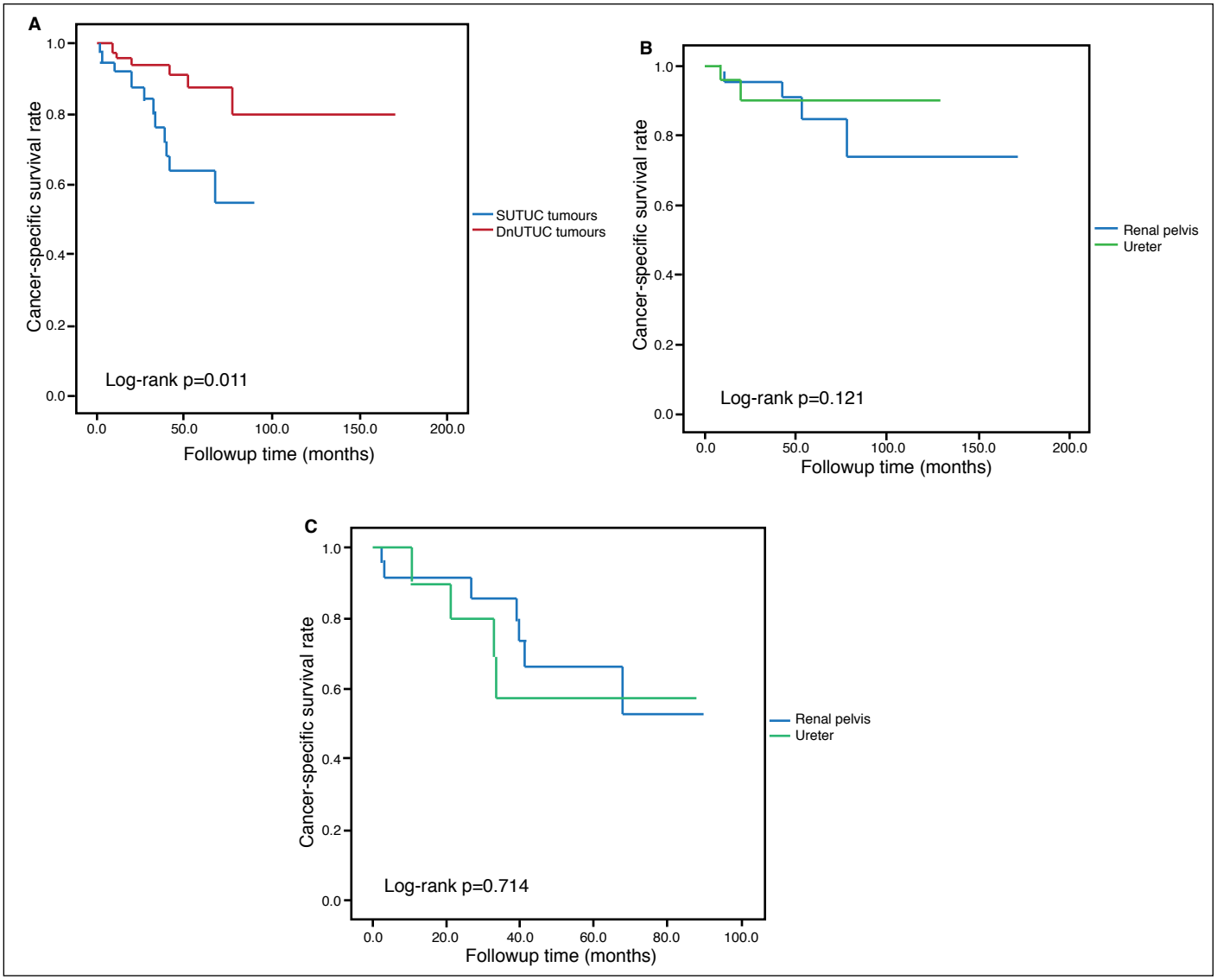

Fig. 2. Cancer-specific survival in ***(A)*** all patients; ***(B)*** de novo upper tract urothelial carcinoma (UTUC) patients; and ***(C)*** secondary UTUC patients.

Discussion

In this cohort, most patients diagnosed with UTUC had de novo disease, without a prior history of bladder carcinoma. Pathological characteristics, including primary tumor stage, grade, and lymph-node involvement were similar between patients with DnUTUC and SUTUC. No clear pathological disparities could be discerned between DnUTUC and SUTUC aside from the higher rate of CIS in SUTUC patients. Although not statistically significant, there was a trend showing that the five-year bladder recurrence rate was higher in the SUTUC group (65.3% vs. 20.5%; p=0.099). Moreover, the five-year CSM rate was significantly worse for SUTUC patients. However, in Cox proportional hazards regression analysis, adjusting for some of the relevant covariates, through the usage of the propensity score, SUTUC was demonstrated to be a significant predictor of bladder recurrence but not of CSM. An important difference demonstrated between the groups was the fact that five DnUTUC patients (4.3%) were diagnosed with Lynch syndrome, an autosomal-dominant genetic syndrome harboring a high risk of colon cancer and other malignancies, including UTUC. This interesting genetic difference between the groups supports the hypothesis that DnUTUC is a distinct entity when compared to SUTUC, which might be more closely related to bladder cancer.

Reconciling whether SUTUC tumors are simply primary bladder recurrences or new primary tumors is a controversial and daunting task. It is known that urothelial carcinoma is a multifocal disease, with at least 30% of patients presenting with multifocal tumors.[13] It has also been shown that abnormalities of the surrounding urothelium are found near the

Table 3. Cox proportional hazards regression analysis predicting bladder recurrence and cancer-specific mortality among all UTUC patients

	Bladder recurrence				Cancer-specific mortality			
	HR	95% CI for OR		p	HR	95% CI for OR		p
		Lower	Upper			Lower	Upper	
Type of UTUC (SUTUC vs. DnUTUC)	3.697	1.689	8.091	0.001	2.246	0.79	6.391	0.129
Matched propensity score (1:2 ratio) with match criteria including age, gender, tumor location, type of surgery, tumor grade, pT stage, pN stage, CIS presence, and LVI presence	3.837	0.971	15.165	0.055	3.63	0.563	23.388	0.175

CI: confidence interval; CIS; carcinoma in situ; DnUTUC: de novo upper tract urothelial carcinoma; HR: hazard ratio; LVI: lymphovascular invasion; OR: odds ratio; SUTUC: secondary upper tract urothelial carcinoma.

base of superficial bladder tumors in 25% of cases,[14] which are intimately associated with recurrence and invasion.[15] In the past, these clinical observations led to the formation of the "field change" concept.[16] According to this concept, exposure to carcinogens results in the independent transformation of epithelial cells to a preconditioned epithelium. This eventually results in the creation of multifocal or metachronous, genetically independent tumors.[16] However, this concept is less accepted today and has been mostly replaced by the theory of clonal origin of multiple urothelial carcinomas.[17] This theory hypothesized that the progeny of a single transformed cell spreads through the urothelium, resulting in topographically and chronologically distinct but genetically related tumors. Therefore, the often-observed multifocality of urothelial carcinomas is a result of intraluminal migration and re-implantation. When the primary tumor initially manifests in the urothelium, cells from which future tumors might arise may already be present, distal from it, along the urothelium. The fact that patients with UTUC have a 22–47% risk of bladder tumors but only a 2–3% risk of contralateral UTUC, and that UTUC develops in only 2–6% of patients with bladder carcinoma[6] favors the clonality concept. If this theory is correct, SUTUC tumors should be prescribed as new primary tumors.[18] However, it is also very likely that these SUTUC tumors originated from the primary bladder tumor (possibly resulting from intra-epithelial migration) and, therefore, the SUTUC tumor may be a recurrence of bladder carcinoma. Furthermore, in the SUTUC patients, it is impossible to delineate whether future bladder recurrences originated from the original bladder tumor or from the SUTUC itself. In any case, due to the inconclusive findings in the literature and until more data is discovered, it is still unclear whether SUTUC is labeled as a recurrence or as a primary tumor.[18]

Our study demonstrates that at least pathologically, there was no difference between DnUTUC and SUTUC except the higher rate of CIS, which could favor the explanation that SUTUC is an extension of bladder carcinoma or represents a recurrence of it. The simple univariate analysis demonstrates a worse CSM rate in SUTUC patients, although this correlation disappeared in the multivariable analysis. Furthermore, although univariate analysis did not demonstrate a statistically significant higher bladder recurrence rate among SUTUC patients, it was seen in the multivariable analysis. Although our goal was to compare UTUC patients with and without bladder cancer history, it was impossible for the propensity score to control for the bladder cancer history. However, the variable of whether the disease was SUTUC or DnUTUC was included in the multivariable model to try and compare between both groups. The multivariable analyses demonstrated that SUTUC was only a predictor of bladder recurrence, which might well be explained by the thought that SUTUC is, in fact, a bladder recurrence, and not a separate disease entity of the upper tract. This study does, to our opinion, suggest there is further room to explore differences between UTUC with and without a history of bladder cancer. Deciphering the true origin of SUTUC will most likely be achieved with use of tumor-specific genetic mutations, as has been done to differentiate between muscle-invasive and non-muscle-invasive bladder tumors[19,20] and between UTUC and bladder carcinoma.[4] Most recently, there have been published data demonstrating UTUC-specific genetic alterations.[21] Applying the methods used in that study could help differentiate between DnUTUC and SUTUC and at least partly answer our questions.

The proportion of DnUTUC patients, tumor location, mean age, and pathological parameters in our cohort were similar to those reported by Cha et al in their multi-institutional study including more than 2200 patients.[22] Our study exhibited a similar rate of chemotherapy usage to that shown in large population-based studies. Such a study, using the Surveillance, Epidemiology and End Results (SEER) Medicare registry between 2002 and 2011, demonstrated use of neoadjuvant and adjuvant chemotherapy in 1.8% and 11.8% of cases, respectively.[23] This is slightly lower than our neoadjuvant rate (3.75–5.4%) but coincides with our adjuvant rate (8.1–12.5%). Our lymph node dissection rate is quite higher than that reported in other studies. Pearce et al reported a rate of 15% in a large, population-based study,[24] considerably lower than our 32.5% rate. Use of laparoscopy in approximately 38% of our cohort is also similar to that reported in previous large studies.[25]

It has been shown that patients who underwent RC are at increased risk of UTUC recurrence.[26] There is no doubt

the fact that in the SUTUC group, 15 patients (40.6%) had undergone RC compared to only two patients (2.5%) in the DnUTUC group had a significant effect on their CSM rates, although we did try to account for that difference by excluding from our analyses all patients who underwent RC prior to SUTUC development.

Ureteral tumor location was demonstrated to predict higher bladder recurrence rates in the DnUTUC group in our cohort. The literature assessing the impact of UTUC tumor location on its outcomes is conflicting. There are several studies showing that ureteral tumors are correlated with recurrence,[27,28] as shown in our DnUTUC group. In contrast, there are a number of studies demonstrating no difference in recurrence rates between UTUC tumors arising from both the renal pelvis and ureter,[29,30] as shown in our SUTUC group.

Our study has several limitations, most notably its retrospective nature and relatively small sample size originating from a single center. The inherent problem of delineating whether SUTUC is a new primary or a bladder tumor recurrence, and the true origin of the ensuing recurrences, whether from the original bladder tumor or from the upper tract, might possibly have caused this group to be contaminated. Adding to this point, it is important to note that in all the KM curves comparing DnUTUC and SUTUC, there is an inherent immortal time bias for the SUTUC patients, as the comparison did not consider the time from bladder carcinoma diagnosis to SUTUC diagnosis. This is especially problematic if the bladder recurrence and CSM reported in our study originated from their primary bladder tumor and not from their SUTUC tumor. Additionally, we lacked data on tumor size, tumor architecture (sessile or papillary), and tumor multifocality, which could have been important parameters, as multifocality, and sessile UTUC tumors have been shown to predict recurrence.[22] Lastly, our followup period of approximately three years was relatively short and this prevented us from appreciating bladder recurrence and CSM outcomes over the long-term. However, this is a hypothesis-generating study and the largest study to date to identify and risk stratify UTUC patients according to DnUTUC and SUTUC type.

Conclusions

The data from our study does suggest that there is further space to explore differences between DnUTUC and SUTUC. It is still unclear whether SUTUC represents a worse disease, however, we strongly support the European guidelines in adhering to the strict followup strategy following surgery, which includes frequent cystoscopies and upper tract imaging in all patients, whether DnUTUC or SUTUC.[6] Whether a difference exists between these two entities leading to a specific and unique followup protocol for each disease type remains to be discovered.

Competing interests: The authors report no competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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Supplementary Table 1. Clinical parameters after propensity score matching (2:1 ratio)

	De novo UTUC	Secondary UTUC	p
Number of patients, n (%)	54 (65%)	29 (35%)	
Mean age, n (SD)	68.8 (12.5)	67.6 (9.6)	0.652
Gender, n (%)			
Male	45 (83.3%)	25 (86.2%)	0.731
Women	9 (16.7%)	4 (13.8%)	
Tumor location n, (%)			
Renal pelvis	34 (63%)	19 (65.5%)	0.817
Ureter	20 (37%)	10 (34.5%)	
Type of surgery, n (%)			
Nephroureterectomy	42 (77.8%)	23 (79.3%)	0.872
Distal ureterectomy	12 (22.2%)	6 (20.7%)	
Pathology grade, n (%)			
Low	20 (37%)	12 (41.4%)	0.698
High	34 (63%)	17 (58.6%)	
Pathological T stage, n (%)			
Ta	31 (57.4%)	16 (55.2%)	
T1	5 (9.3%)	3 (10.3%)	0.96
T2	5 (9.3%)	3 (10.3%)	
T3	12 (22.2%)	7 (24.1%)	
T4	1 (1.9%)	0	
Pathological N stage, n (%)			
N0	11 (20.4%)	5 (17.2%)	
N1	0	1 (3.4%)	0.536
N2	4 (7.4%)	3 (10.3%)	
NX	39 (72.2%)	20 (69%)	
CIS present, n (%)	13 (24.1%)	8 (27.6%)	0.726
Lymphovascular invasion present, n (%)	8 (14.8%)	5 (17.2%)	0.772

CIS: carcinoma in situ; SD: standard deviation; UTUC: upper tract urothelial carcinoma.