



Original Article

Long-term survival of upper tract urothelial carcinoma patients in a tertiary care hospital

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Abstract

Objective: Upper urinary tract urothelial carcinoma (UTUC) is an uncommon but rapidly progressive disease associated with a high mortality rate. Despite the advancement in surgical and medical treatment during the last decade, long-term clinical data pertinent to UTUC are still limited in Thailand. The objectives of this study were to identify the long-term survival rate and factors affecting the survival of UTUC patients.

Materials and Methods: We reviewed medical records of UTUC patients treated at King Chulalongkorn Memorial Hospital from 2004 to 2019. We calculated 5-year survival rate using the Kaplan-Meier method and investigated its correlation with various clinicopathological factors through the Cox hazard regression model.

Results: One hundred and twenty-seven UTUC patients were included in this study. There was a slight predominance of females (55.1%), and the mean age at diagnosis was 68.2 years. The majority of patients were TNM stage I (43.3%) followed by stage III (26.9%). The 5-year overall and cancer-specific survival rates were 62.2% and 75.6%, respectively. Based on univariable analysis, TNM stage, pathological T stage, pathological N stage, and lymph node dissection status were associated with the overall survival and cancer-specific survival. However, none of these factors remained statistically significant in the multivariate analysis.

Conclusion: The 5-year overall survival rate of UTUC patients was 62.2%. TNM stage, pathological T stage, pathological N stage, and lymph node dissection status were associated with the overall survival. A further study with a higher population number is warranted to add weight to these findings and investigate their potential clinical use further.

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Introduction

Upper tract urothelial carcinoma (UTUC) or transitional cell carcinoma is cancer of the urothelial lining of the upper urinary tract which is taken to consist of the renal calyces, renal pelvis, and ureter. Although only found in 5-7% of all renal cancer patients,¹ UTUC is associated with a poor prognosis due to a rapid progression, delayed diagnosis, and treatment complexity. Risk factors for UTUC include smoking and contact with aromatic amines.² Studies have shown that 60% of UTUC patients were diagnosed with invasive or high-grade tumors compared to 15-25% of those with urinary bladder cancer.^{3,4}

The fundamental basis of UTUC treatment is radical nephroureterectomy with bladder cuff excision and lymph node dissection. The traditional open surgical technique has been increasingly replaced by minimally invasive techniques such as laparoscopic or robotic-assisted approaches, which offer rapid recovery with lower levels of morbidity. Among patients presenting with locally advanced or metastatic disease, adjuvant treatment with radiation, systemic chemotherapy, or even immunotherapy is usually offered.

Since the incidence of UTUC is low, and patients received treatment in different centers, there is a lack of long-term clinical data in Thailand. Hence, the authors conducted this study to identify the survival rate of UTUC patients and explore clinicopathologic factors associated with long-term survival in a single center.

Materials and Methods

This is a retrospective analysis of UTUC patients older than 18 years old who were treated at King Chulalongkorn Memorial Hospital, Bangkok, Thailand, from January 2004 to November 2019. Approval from the institutional review board with a waiver of informed consent was obtained prior to the study (IRB No. 493/62). The authors searched for eligible patients from the electronic medical records by using the 10th International Classification of Diseases (ICD-10) codes of "C64 (malignant neoplasm of kidney, except renal pelvis)", "C65 (malignant neoplasm of renal pelvis)", and "C66 (malignant neoplasm of ureter)". Patients with confirmed diagnoses of UTUC from histopathology or cytopathology were included in the study. The authors excluded patients with a history of bladder cancer, patients with concurrent

bladder cancer or other malignancies at the time of UTUC diagnosis, and patients with inadequate medical records.

Demographic data were collected including age at diagnosis, sex, body mass index, and comorbidities. The date of diagnosis was defined as the date of pathological or cytological confirmation of UTUC. The clinical presentation was defined as symptomatic or asymptomatic, and computed tomography or magnetic resonance imaging were utilized for the clinical diagnosis. Data regarding the surgical procedure, surgical approach, and lymph node dissection were collected.

Tumor characteristics, including size and location, were primarily classified based on histopathological findings. Tumor size was measured at the maximal dimension and tumors were divided into < 2 cm and \geq 2 cm. Tumor location was categorized as renal calyx, renal pelvis, proximal ureter, middle ureter, and distal ureter. Multifocal tumor was recorded if the tumor was present in at least two locations. Histopathological data including tumor grade, T-stage, N-stage, and TNM stage grouping were reported in accordance with the 8th edition of the American Joint Committee on Cancer TNM staging for renal pelvis and ureter. In cases where histopathological data was unavailable, tumor characteristics and clinical staging were estimated based on findings from computed tomography or magnetic resonance imaging.

Living status, the date of death, and cause of death were obtained from the hospital medical records. If the data was unavailable, the authors interviewed the patient's family by telephone or obtained the data from the Bureau of Registration Administration. Overall and cancer specific survivals (reported in months) were calculated from the date of diagnosis to the date of death by all-causes, and cancer-specific death, respectively.

Continuous variables were reported as mean \pm standard deviation, and categorical variables were presented as frequency and percentage. Overall and cancer-specific survival rates were estimated using the Kaplan-Meier method. Each clinicopathological factor was correlated to overall and cancer-specific survival by univariate and multivariate analysis using the Cox regression. Statistical analysis was performed with IBM SPSS Statistics version 22.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was considered at $p < 0.05$.



Results

Medical records of 207 UTUC patients were reviewed. Fifty-eight patients were excluded due to a previous or concurrent diagnosis of bladder cancer. Six patients were diagnosed with other concurrent malignancies and were also excluded. Sixteen patients were excluded due to incomplete data collection. The remaining total of 127 patients was analyzed in this study.

Out of all patients, there was a slight predominance of females (55.1%) over males (44.9%). The

mean age at UTUC diagnosis was 68.2 ± 11.9 years, and the mean body mass index was 23.1 ± 4.4 kg/m². The most common comorbidities were hypertension (64.6%), diabetes mellitus (28.3%), and dyslipidemia (25.2%). Almost all patients (89.8%) were symptomatic at the initial presentation, with gross hematuria (86.0%) as the most common presenting symptom, following by flank pain or abdominal pain (14.9%) (Table 1).

Three patients did not undergo surgical treatment due to an advanced stage of disease.

Table 1. Demographics and perioperative data of UTUC patients

Parameters (n = 127)		Value
Preoperative data (n = 127)	Age at diagnosis, mean \pm SD (years)	68.2 \pm 11.9
	Sex, n (%)	
	- Male	57 (44.9)
	- Female	70 (55.1)
	Body mass index, mean \pm SD	23.1 \pm 4.4
	Comorbidity, n (%)	
	- Diabetes mellitus	36 (28.3)
	- Hypertension	82 (64.6)
	- Dyslipidemia	32 (25.2)
	- Ischemic heart disease	9 (7.1)
	- Stroke/CVA	9 (7.1)
	- COPD	2 (1.6)
	Clinical presentation, n (%)	
	- Asymptomatic	13 (10.2)
	- Gross hematuria	98 (86.0)
	- Microscopic hematuria	2 (1.8)
	- Flank pain/abdominal pain	17 (14.9)
	- Palpable abdominal mass	3 (2.6)
	Laterality, n (%)	
	- Right	64 (50.4)
	- Left	57 (44.9)
	- Bilateral	6 (4.7)
Intraoperative data (n = 124)	Aim of surgery, n (%)	
	- Curative aim	117 (94.4)
	- Palliative aim	7 (5.6)
	Surgical procedure, n (%)	
	- Radical nephroureterectomy with bladder cuff excision	121 (97.6)
	- Radical nephrectomy	1 (0.8)
	- Distal ureterectomy	2 (1.6)
	Surgical approach, n (%)	
	- Open approach	70 (56.5)
	- Laparoscopic approach	54 (43.5)
	Lymph node dissection, n (%)	
	- Performed	25 (20.2)
	- Not performed	99 (79.8)

UTUC = upper tract urothelial carcinoma, SD = standard deviation, CVD = cerebrovascular accident, COPD = chronic obstructive pulmonary disease

Table 2. Pathological data of UTUC patients

Parameters (n = 127)	Value
Tumor size (cm), mean±SD	4.3±2.9
Tumor size, n (%)	
- < 2 cm	20 (15.7)
- ≥ 2 cm	107 (84.3)
Tumor location, n (%)	
- Renal calyx	50 (40.3)
- Renal pelvis	60 (48.4)
- Proximal ureter	33 (26.6)
- Middle ureter	15 (12.1)
- Distal ureter	38 (30.6)
Multifocal tumor, n (%)	
- Absence	78 (61.4)
- Presence	49 (38.6)
Tumor grade, n (%)	
- Low grade	22 (17.3)
- High grade	105 (82.7)
Concurrent upper tract CIS, n (%) (n = 124)	
- Absence	114 (91.9)
- Presence	10 (8.1)
T-stage, n (%)	
- Ta	24 (18.9)
- Tis	1 (0.8)
- T1	31 (24.4)
- T2	20 (15.7)
- T3	42 (33.1)
- T4	9 (7.1)
N-stage, n (%)	
- N0	112 (88.2)
- N1	4 (3.1)
- N2	10 (7.9)
- N3	1 (0.8)
M-stage, n (%)	
- M0	123 (96.9)
- M1	4 (3.1)
Distant metastasis, n (%)	
- Liver	3 (75)
- Lung	1 (25)
TNM stage grouping, n (%)	
- Stage 0is	1 (0.8)
- Stage I	55 (43.3)
- Stage II	19 (15.0)
- Stage III	33 (25.9)
- Stage IV	19 (15.0)

UTUC = upper tract urothelial carcinoma,
SD = standard deviation, CIS = carcinoma in situ

Out of 124 patients who underwent surgical treatment, curative surgery was the aim in 117 patients (94.4%). Radical nephroureterectomy with bladder cuff excision was performed in

Table 3. Survival data of UTUC patients

Parameters (n = 127)	Value
Living status, n (%)	
- Alive	62 (48.8)
- Dead	65 (51.2)
Cause of death, n (%) (n = 65)	
- UTUC-related causes	38 (58.5)
- Other causes	27 (41.5)
Overall survival rate %	48.8
- 1-year overall survival rate	81.9
- 5-year overall survival rate	62.2
Cancer-specific survival rate %	70.1
- 1-year cancer-specific survival rate	88.2
- 5-year cancer-specific survival rate	75.6
Overall time to death (months), mean (95% confidence interval)	93.8 (78.5 to 109.0)
Cancer-specific time to death (months), mean (95% confidence interval)	129.3 (113.0 to 145.7)
Follow-up duration (months), mean (95% confidence interval)	49.7 (0.3-187.4)

UTUC = upper tract urothelial carcinoma

the majority of cases (97.6%). An open surgical approach (56.5%) was used more commonly than laparoscopy (43.5%). Lymph node dissection was performed in 25 patients (20.2%). One patient received neoadjuvant chemotherapy, 17 patients received adjuvant chemotherapy, and 16 patients underwent adjuvant postoperative radiation (Table 1).

The mean tumor size was 4.3±2.9 cm, with 84.3% of the tumors being larger than 2 cm. In the majority of cases the tumor was located in the renal pelvis (48.4%), followed by the renal calyx (40.3%) and the distal ureter (30.6%). Multifocal tumors were found in 38.6% of the patients. High grade tumors were found in 82.7%, and concurrent upper tract CIS were found in 8.1%. The most common T-stage was T3 (33.1%), followed by T1 (24.4%), and Ta (18.9%). Lymph node status was negative for most patients (88.2%); however, this data was only available in one-fifth of the patients. The proportion of TNM stage grouping was 0.8%, 43.3%, 15.0%, 25.9%, and 15.0% for stage 0is, I, II, III, and IV, respectively (Table 2).

At the end of the study, 62 patients were alive, and 65 patients were dead (38 had died from UTUC-related causes, and 27 from other causes). The median follow-up duration was 49.7 months. The mean overall survival was 93.8 months, and the mean cancer-specific survival

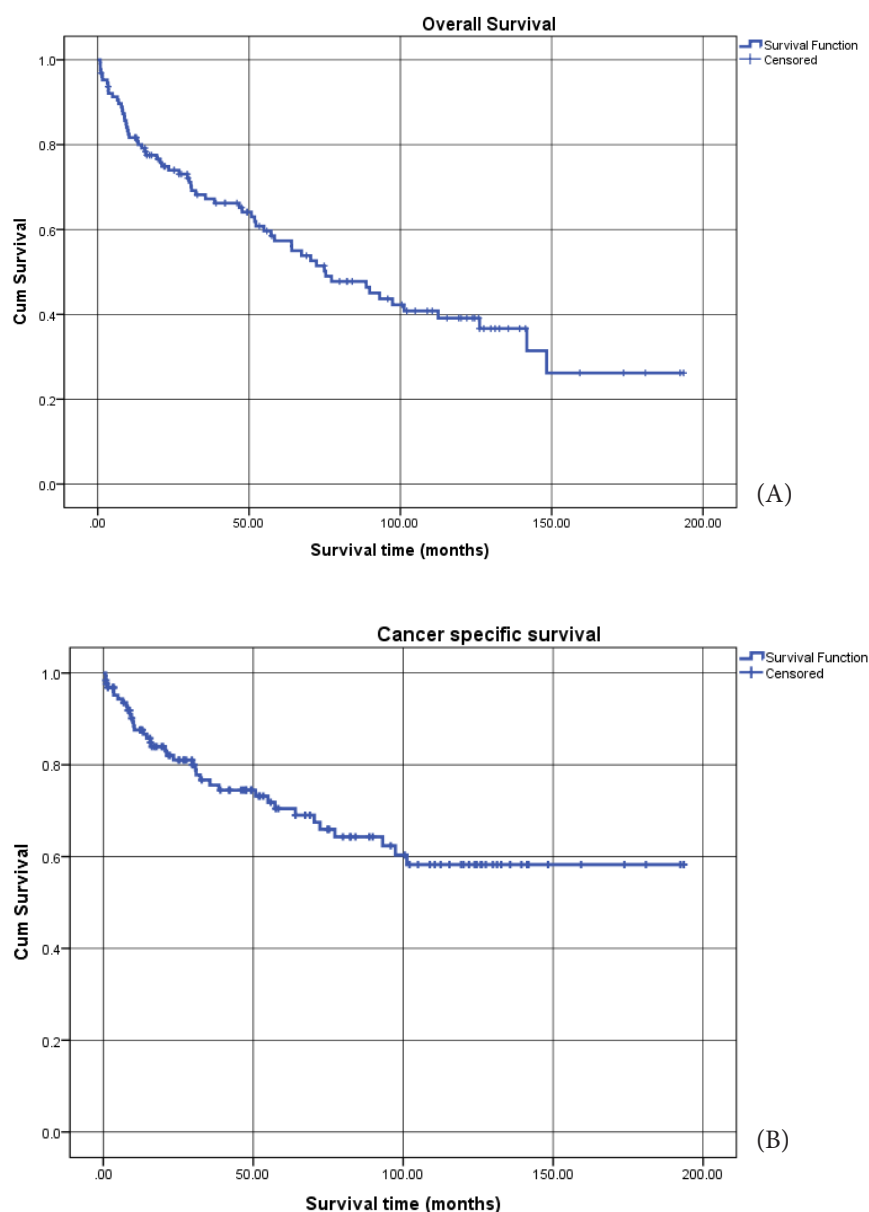


Figure 1. Kaplan-Meier plot of overall survival (A) and cancer-specific survival (B)

was 129.3 months (Table 3). The Kaplan-Meier plot showed an overall survival rate of 48.8% and a cancer-specific survival rate of 70.1%. The 5-year overall and cancer-specific survival rates were 62.2% and 75.6%, respectively (Figure 1).

Univariate analysis using Cox regression was performed to ascertain any correlation between each clinicopathological factor and the overall and cancer-specific survivals. Overall survival showed a significant correlation with lymph node dissection status ($p = 0.037$), T-stage ($p = 0.034$), N-stage ($p = 0.000$), and TNM stage grouping ($p = 0.034$). Cancer-specific survival showed a significant correlation with lymph node dissection status ($p = 0.010$), tumor grade ($p = 0.016$),

T-stage ($p = 0.001$), N-stage ($p = 0.000$), and TNM stage grouping ($p = 0.001$) (Table 4). Subsequently, a prediction model with multivariate analysis was performed involving significant clinicopathological factors identified from the univariate analysis. However, none of these factors remained statistically significant when adjusted with the multivariable analysis (Table 5).

Discussion

UTUC is an uncommon disease with limited long-term data on survival. It accounts for 5-10% of all urothelial cancers with an estimated annual incidence of 1-2 cases per 100,000 in the United States.¹ The recorded incidence has been

Table 4. Univariate analysis of overall and cancer-specific survivals

Parameters	Overall survival, p-value	Cancer-specific survival, p-value
Sex (male versus female)	0.125	0.181
Surgical approach (open versus lapa-rosopic approach)	0.133	0.141
Lymph node dissection (performed versus not performed)	0.037*	0.010*
Tumor size (< 2 cm versus ≥ 2 cm)	0.212	0.090
Tumor location (renal calyx/renal pelvis versus proximal/middle/distal ureter)	0.428	0.713
Multifocal tumor (absence versus presence)	0.255	0.589
Tumor grade (low grade versus high grade)	0.344	0.016*
Concurrent upper tract CIS (absence versus presence)	0.965	0.435
T-stage (Ta/Tis/T1 versus T2-T4)	0.034*	0.001*
N-stage (N0 versus N1-N3)	0.000*	0.000*
TNM stage grouping (stage 0is/stage I versus stage II-IV)	0.034*	0.001*

*, statistically significant, CIS = carcinoma in situ

Table 5. Multivariate analysis of overall and cancer-specific survivals

Parameters	Overall survival, P-value (hazard ratio)	Cancer-specific survival, P-value (hazard ratio)
Tumor grade (low grade versus high grade)	N/A	0.132
T-stage (Ta/Tis/T1 versus T2-T4)	0.769	0.732
N-stage (N0 versus N1-N3)	0.268	0.819
Lymph node dissection (performed versus not performed)	0.752	0.937

increasing during the last few decades mainly due to improvements in imaging, diagnostic endoscopy, and cytopathology. Epidemiological data in Thailand about this condition is markedly limited mainly due to rarity of the disease and inadequacy of the national tumor registry. In addition, UTUC is sometimes under-reported or miss-interpreted due to the difficulty in diagnosis.

The data for this study were retrospectively collected over 16 years and have shown some interesting epidemiological findings. We found the ratio between male and female patients to be similar (44.9% versus 55.1%). In contrast, other studies from Western countries have shown the majority of patients, ranging from 64 to 68.4%, to be male.⁵⁻⁷ One study from Thailand found 61.5% out of 65 UTUC patients undergoing radical nephroureterectomy to be male.⁸ Another study from central China found 53.7% out of 439 UTUC patients to be male.⁹ Hypothetically, there could be a genetic gender predilection among

different ethnicities, with a slightly lower male predominance in Asia. Another possible explanation may be the exclusion criteria used in our study. We excluded all patients with a concurrent or subsequent diagnosis of bladder cancer. These were predominantly male. In our study, the most common tumor location was the renal pelvis, following by the renal calyx. Multifocal tumors were found in 38.6% of patients, this incidence being higher than in a previous study by Favaretto et al., which showed an incidence of 25%.¹⁰

Based on the observations from 127 UTUC patients from 2007 to 2019, we calculated a 5-year cancer-specific survival of 75.6%. This survival rate is comparable to findings from other previous studies. Wheat et al. retrospectively reviewed 1,387 UTUC patients undergoing radical nephroureterectomy from 13 institutions between 1987 and 2007. They found a cancer-specific survival of 85% at 1 year, 75% at 3 years and 70% at 7 years.⁶ Munoz and Ellison identified 9,072 UTUC



patients in a Surveillance, Epidemiology and End Results (SEER) program from 1973 to 1996. They demonstrated a 5-year cancer-specific survival of 75%.¹¹ Interestingly, although the surgical techniques and adjuvant treatment modalities have been improved during the last two decades, the cancer-specific survival is still unchanged. Whether this finding results from more aggressive tumor behavior or not is still under debate.

Several prognostic factors for cancer-specific survival have been identified from the univariate analysis. They included the lymph node dissection status, tumor grade, T-stage, N- stage, and TNM stage grouping. However, T-stage and TNM stage grouping were significantly correlated and together could be a covariate. Thus, we decided not to include TNM stage grouping in the further analysis. The subsequent multivariate analysis revealed no statistically significant factors. However, contrary to our findings, a large retrospective cohort study of 13,800 UTUC cases from the SEER database reported multiple factors significantly associated with poorer overall survival using multivariate analysis. These factors included increasing patient age, male gender, black non-Hispanic race, bilateral UTUC, and regional or distant disease.⁷ Another study by Wheat et al. found that concomitant CIS was predictive of cancer specific mortality in 1,387 patients with organ confined UTUC.⁶ However, in their study, 26.7% of patients had concomitant CIS, compared to only 8.1% in our study. In addition, Wheat et al. also included patients with a previous history of bladder cancer in their analysis, which may have a different natural history.

We found that different surgical approaches, specifically open or laparoscopic technique, did not affect long-term survival of the patients. This finding is consistent with the study by Taweemonkongsap et al., which reported similar 2-year cancer-specific survivals of 92.5% and 86.3% after open and laparoscopic techniques, respectively.¹²

Some limitations were encountered in this study. The retrospective nature of the design inevitably leads to incomplete data collection and selection bias. Owing to the rarity of the disease, the sample size is relatively limited, which may negatively affect the statistical power of the data. Moreover, the decision as to whether to perform lymph node dissection (LND) was in accordance

with the discretion of each surgeon, and the data regarding the LND template was limited. We also did not account for other treatment modalities such as radiation, systemic chemotherapy, or further management for distant metastasis, which could have an effect on patient survival. To generalize the results to the UTUC population, a larger scale multi-center prospective study should be conducted to add weight to these findings.

Conclusions

The 5-year overall survival rate of UTUC patients was 62.2%. TNM stage, pathological T stage, pathological N stage, and lymph node dissection status were associated with the overall survival. Further study with a higher population number may be conducted to confirm this association.

Conflict of Interest

The authors declare no conflict of interest.

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