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Prognostic Implications of Postoperative Serum CYFRA Levels in Upper Tract Urothelial Carcinoma

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Background: Current guidelines lack recommendations for serum tumor markers in patients with upper tract urothelial carcinoma (UTUC) undergoing radical nephroureterectomy (RNU). This study assessed the potential of the postoperative serum C-terminus of cytokeratin 19 (CYFRA21-1, CYFRA) level, hereafter referred to as poCY, as a predictor of early progression in patients treated with RNU.

Methods: Overall, 117 patients were categorized into the high group (HG) or low group (LG) based on a poCY cutoff level of 3.5 ng/mL after excluding those who did not meet the inclusion criteria. Kaplan-Meier curves and log-rank tests were used to measure cancer-specific survival (CSS) and progression-free survival (PFS) rates. Multivariate analysis was performed using the Cox proportional hazards model.

Results: During a median follow-up of 34 months, the 5-year CSS and PFS rates were 79% and 66%, respectively. The HG had a significantly worse CSS and 2-year PFS than the LG. Multivariate analyses identified poCY and lymph node involvement (LNI) as independent prognostic factors. Regarding the 2-year PFS, poCY, LNI, and resection margin status (RM) emerged as independent prognostic factors.

Conclusions: poCY, LNI, and RM predicted early progression following RNU in patients with UTUC. Patients with elevated poCY may benefit from adjuvant chemotherapy, irrespective of their pathological findings. (J Nippon Med Sch 2025; 92: 321–330)

Key words: radical nephroureterectomy, biomarker, postoperative progression, urothelial carcinoma, CYFRA

Introduction

Urothelial carcinoma (UC) predominantly affects the urinary bladder, though 5-10% of cases involve the upper urinary tract (UTUC). For UTUC, radical nephroureterectomy (RNU) is standard, but diagnosis often occurs at advanced stages, with up to 30% of muscle-invasive UTUC cases presenting with lymph node involvement at diagnosis, leading to 5-year survival rates of 50-80%[1–6]. The effectiveness of perioperative chemotherapy, established in lower tract UC, remains uncertain for UTUC. Advances in cancer therapy have introduced new perioperative treatments and recurrence management options for UTUC, including platinum-based chemotherapy as standard care. Recent approvals of immune checkpoint inhibitors and targeted therapies like pembrolizumab, avelumab, enfortumab vedotin, and erdafitinib have improved outcomes[7–10]. Despite these advances, reliable markers for recurrence prediction are scarce, with radiological staging challenges prompting a preference for adjuvant over neoadjuvant chemotherapy (NAC), leading to potential overtreatment[11,12].

This study investigates postoperative serum CYFRA

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https://doi.org/10.1272/jnms.JNMS.2025_92-404
Journal Website (https://www.nms.ac.jp/sh/jnms/)

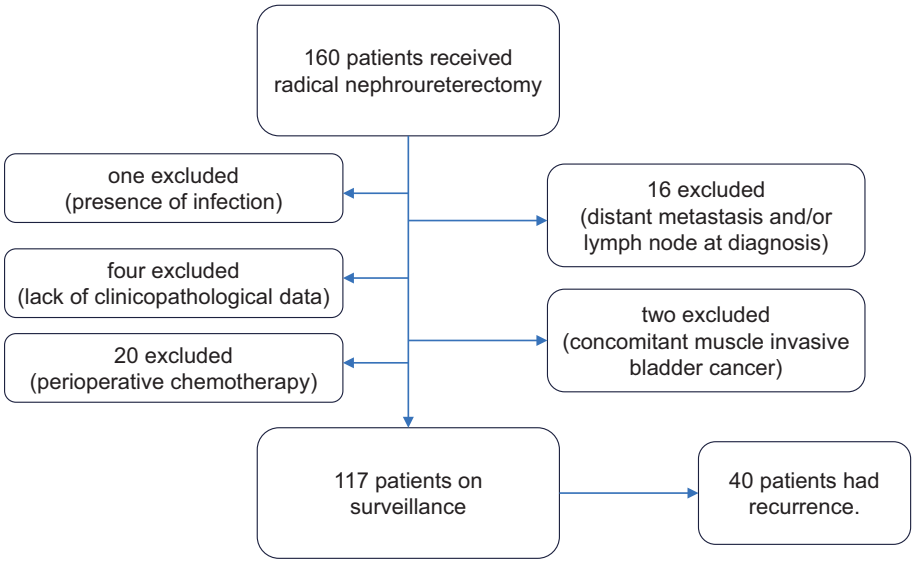

Fig. 1 Patient selection flowchart

(poCY), a marker derived from CK19, as a potential predictor of survival and recurrence in UTUC patients post-RNU. We aim to correlate poCY levels with clinicopathological parameters and treatment outcomes, thus helping to identify patients who might benefit from intensified postoperative therapy.

Material and Methods

1. Patients and Study Design

We retrospectively reviewed the medical records of patients who underwent RNU for UTUC from 2006 to 2016 at Nippon Medical School Hospital. A total of 160 patients were initially considered for our analysis. However, we excluded 43 patients based on predefined criteria to ensure the integrity of the study results. Specifically, 16 patients were excluded at the outset due to the presence of distant metastasis or LNI at diagnosis, which inherently predisposes them to early disease progression, making them unsuitable for observational purposes. One patient was excluded because of an active infection at the time of diagnosis. Since sCYFRA levels are known to elevate in the presence of active urinary infections, this could confound the evaluation of sCYFRA as a predictor of UTUC recurrence postoperatively. Two patients were concurrently diagnosed with muscle-invasive bladder cancer, which could also result in elevated sCYFRA levels, thereby hindering the accurate assessment of its levels attributable solely to UTUC. Additionally, 20 patients were excluded because they received perioperative chemotherapy, a factor that could significantly alter postoperative outcomes and affect the recurrence of UTUC.

Following these inclusion criteria allowed for a refined cohort of 117 patients with non-metastatic UTUC (Ta-4N0 M0). This enabled the more precise evaluation of factors associated with early recurrence after RNU in localized UTUC (**Fig. 1**).

Laparoscopic RNU, in recent cases, was principally performed via a retroperitoneal approach, after which, the bladder cuff was removed using an extravesical incision. The extent of LND varied; in general, the paraaortic, paracaval, or interaortic caval LNs from the hilus to the inferior mesenteric artery were removed in cases involving the renal pelvis and proximal ureteral tumors. For mid-ureteral tumors, LNs from the renal hilus to the bifurcation of the common iliac artery and the ipsilateral pelvic LNs were removed. For lower ureteral tumors, ipsilateral pelvic LNs were removed. The pathological stage was determined according to the 2009 tumor-node-metastasis classification system. The tumor grade was assigned according to the 1999 World Health Organization classification. Post-RNU, the patients were followed up every 3 months with physical examination, blood test, computed tomography scan, cystoscopy, and urine cytology examinations for 2 years and every 6 months after that. The poCY measurements were obtained 4-8 weeks postoperatively in all patients, and they were categorized into two groups based on two levels of poCY. One threshold was 3.5 ng/mL, as defined by Pujol et al.[13], who analyzed poCY levels in healthy volunteers while considering the squamous lung cancer criteria[14]. The second poCY threshold was defined according to the ROC curve calculated using our cohort.

In the postoperative follow-up, cases with imaging-confirmed recurrence were treated with systemic chemo-

therapy based on patient treatment preferences and the judgment of the attending physician. In this study, we identified 40 recurrences among 116 patients following RNU. These recurrent cases were further examined separately, and clinical information, metastasis locations, and details of systemic chemotherapy regimens were retrospectively collected.

2. Statistical Analysis

Table 1 presents the patient characteristics. The background parameters of HG and LG were compared using Fisher's exact test (**Table 2**). The association of poCY levels with PFS, CSS, and OS was assessed using the Kaplan-Meier method. Additionally, the log-rank test was used to assess significant differences in survival outcomes between groups categorized by each CYFRA level (cutoff value: 3.5 ng/mL and CYFRA calculated by ROC curve). The poCY measurements were obtained in 117 patients who underwent RNU. Univariate and multivariate Cox regression analyses were performed to identify independent factors for RFS, CSS, and OS. To determine the independent prognostic significance of CYFRA in predicting disease progression and OS in these patients, multivariate analysis was conducted considering various postoperative factors, such as surgical margin status, LVI, pT stage, and Furman grade. Continuous variable Cox regression analyses were also performed to assess the impact of postoperative poCY levels on PFS, CSS, and OS to quantitatively evaluate the relationship between incremental increases in poCY levels and risks for each mortality.

Additionally, for cases that recurred postoperatively, we examined the relationship between the duration from recurrence to cancer specific death (rCSS) and poCY using Kaplan-Meier curves and compared rCSS between the two groups using the log-rank test. Furthermore, we investigated rCSS according to different regimens of subsequent systemic therapy.

All data were analyzed using IBM SPSS Statistics Software for Windows, version 20 (IBM Corp., Armonk, N.Y., USA). Significant differences were considered at a one-sided p-value of < 0.05.

3. Ethics Approval

The study was approved by the Institutional Review Board of Nippon Medical School (approval number: O-2021-080) and conducted in accordance with the Declaration of Helsinki.

Results

Table 1 presents the clinical and pathological characteristics of 117 patients with UTUC. The patients' median age was 71 (range: 50-78) years, and 86 (73.5%) of them were men. Thirty (25.6%) patients underwent open RNU with lymph node dissection (LND), and 87 (74.4%) underwent laparoscopic RNU without LND. Pathological data showed that 22 (18.8%) patients had lymphovascular invasion (LVI) and that 28 (23.9%) had positive resection margins. Of the 30 patients who underwent open RNU with LND, 14 (46.7%) had positive lymph nodes (LNs). The patients were categorized into the following two groups based on their poCY levels (threshold of. 3.5 ng/mL): 92 (79%) in the low group (LG) and 25 (21%) in the high group (HG). Fisher's exact test revealed no statistically significant differences between the two groups in terms of background patient characteristics (**Table 2**).

For the entire cohort, the 2- and 5-year PFS rates were 73% and 66%, respectively, and the 2- and 5-year cancer-

Table 1 Background patient characteristics

n (%)	Total (n=117)	%
Sex		
Male	86	73.5
Female	31	26.5
Median age, median (range), years	71	50–78
Grade		
G1, 2	48	41.0
G3	69	59.0
T stage		
≤pT1	41	35.0
pT2	31	26.5
pT3	37	31.6
pT4	8	6.8
Surgical method		
Open surgery with LND	30	25.6
Laparoscopic surgery	87	74.4
Primary tumor location		
Kidney	62	53.0
Ureter	55	47.0
Histological subtype		
Yes	14	12.0
No	103	88.0
Pathological data on RNU		
Lymph node involvement		
Negative	16	13.7
Positive	14	12.0
Lymphovascular invasion		
Negative	94	38.5
Positive	22	61.5
Resected margin		
Negative	89	76.1
Positive	28	23.9

LND: lymph node dissection, RNU: radical nephroureterectomy

Table 2 Background patient characteristics of high and low poCY groups

n (%)	Total (n=117)	%	High poCY group (n=25)	%	Low poCY group (n=92)	%	p-value
Sex							0.301
male	86	73.5	21	84.0	65	70.7	
female	31	26.5	4	16.0	27	29.3	
Median age, median (range)	71	50–78	73	52–75	70	50–78	0.445
Grade							0.635
G1, 2	48	41.0	10	40.0	38	41.3	
G3	69	59.0	15	60.0	54	58.7	
T stage							1.000
<pT2	41	35.0	8	32.0	33	35.9	
>=pT2	76	65.0	17	68.0	59	64.1	
Surgical method							0.785
Open surgery with LND	30	25.6	6	24.0	24	26.1	
Laparoscopic surgery	87	74.4	19	76.0	68	73.9	
Primary tumor location							0.230
Kidney	62	53.0	15	60.0	47	51.1	
Ureter	55	47.0	10	40.0	45	48.9	
Histological characteristics							0.712
UC with subtype	14	12.0	4	16.0	10	10.9	
UC without subtype	103	88.0	21	84.0	82	89.1	
Pathological data on RNU							
Lymph node involvement							0.644
Negative	16	13.7	3	50.0	13	54.2	
Positive	14	12.0	3	50.0	11	45.8	
Lymphovascular invasion							0.566
Negative	95	81.2	18	72.0	77	83.7	
Positive	22	18.8	7	28.0	15	16.3	
Resected margin							0.053
Negative	89	76.1	18	72.0	71	77.2	
Positive	28	23.9	7	28.0	21	22.8	

LND: lymph node dissection, poCY: postoperative serum level of the C-terminus of cytokeratin 19, UC: urothelial carcinoma, RNU: radical nephroureterectomy

specific survival (CSS) rates were 87% and 79%, respectively (**Figure 2a and b**). During the median follow-up period of 34.0 (1-152) months, 39 (35%) patients died. The 2-year PFS rate in the HG was 48%, which was significantly lower than that in the LG (74%) (p = 0.003) (**Fig. 3a**). Furthermore, the 5-year CSS rate in the HG was 51%, which was significantly lower than that in the LG (86%) (p = 0.002) (**Fig. 3b**).

Univariate analysis revealed that tumor grade (hazard ratio [HR], 2.0; p = 0.029), poCY level (HR, 2.9; p = 0.035), LNI (HR, 7.5; p < 0.001), LVI (HR, 2.3; p = 0.020), and resection margin status (RM; HR, 3.7; p < 0.001) were significant factors for 2-year PFS. In the multivariate analysis, poCY level (HR, 2.3; 95% confidence interval [CI] = 1.2-5.3; p = 0.038), LNI (HR, 5.8; 95% CI = 1.2-27.8; p = 0.003), and RM (HR, 3.4; 95% CI = 1.3-8.7; p = 0.010) were identified as independent factors for the 2-year PFS (**Table 3**).

In contrast, univariate analysis showed that tumor grade (HR, 9.8; p = 0.028), pT stage (HR, 9.9; p = 0.026), poCY level (HR, 5.4; p = 0.002), LNI (HR, 8.5; p = 0.003), and RM (HR, 5.6; p = 0.001) were significant factors for the 5-year CSS. In the multivariate analysis, the poCY level (HR, 5.2; 95% CI = 1.7-16.1; p = 0.009) and LNI (HR, 6.5; 95% CI = 1.4-49.9; p = 0.004) were independent prognostic factors for the 5-year CSS (**Table 3**).

Continuous variable Cox regression analyses demonstrated that each unit increase in postoperative CYFRA levels significantly impacted key survival outcomes: a 1.1% increase in the risk of disease progression or recurrence for PFS (B = 0.011, HR = 1.011, p = 0.003), a 1.2% increase in cancer-specific mortality risk for CSS (B = 0.012, HR = 1.012, p = 0.002), and a 1.1% increase in overall mortality risk for OS (B = 0.011, HR = 1.011, p = 0.003).

Table 4 presents the background characteristics of the

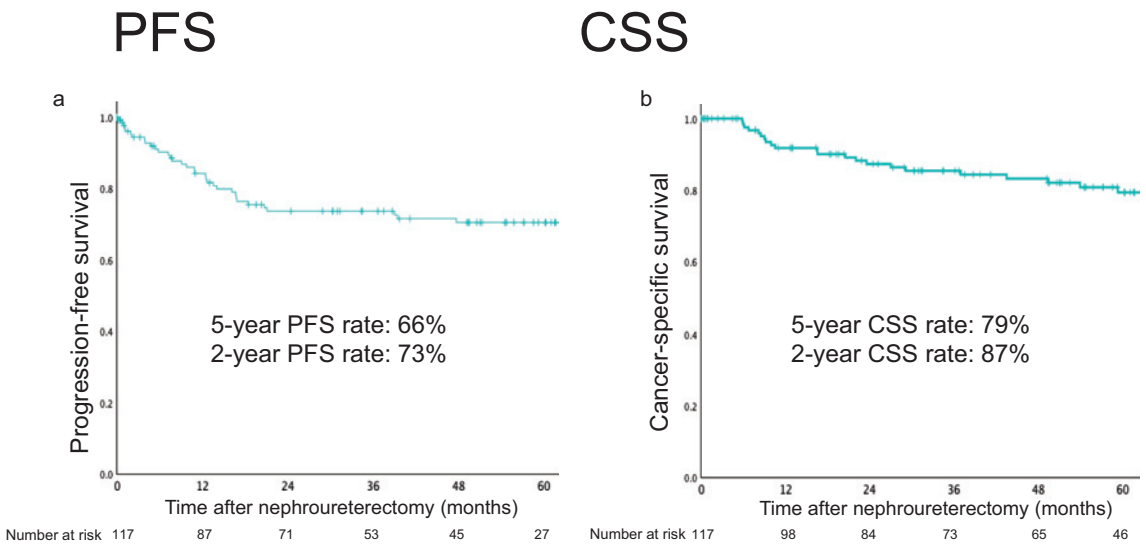

Fig. 2 Progression-free survival (PFS) (a) and cancer-specific survival (CSS) (b) rates in all cohorts. (a) Kaplan–Meier curve of PFS rate and months after radical nephroureterectomy. The 2- and 5-year PFS rates were 73% and 66%, respectively. (b) Kaplan–Meier curve of CSS rate and months after radical nephroureterectomy. The 2- and 5-year CSS rates were 87% and 79%, respectively.

patients with recurrent cases. Forty patients had recurrence, of whom 26 (65%) were male, with a median age of 74 (range: 52-75) years. The primary tumor location was the renal pelvis in 18 (45%) patients. LNI was observed in 10 (25%) patients, subtype histology in 7 (17.5%), LVI positivity in 10 (25%), RM positivity in 12 (30%), and poCY positivity in 10 (25%). Metastases included the LNs in 23 (57.5%) patients; the liver in 6 (15%); the lungs in 5 (12.5%); and bone, local recurrence, and peritoneal seeding in 2 (5%) each. Among the patients with recurrence, 23 (57.5%) underwent chemotherapy, with 18 receiving gemcitabine + cisplatin (GC) and 5 (12.5%) receiving ifosfamide + paclitaxel + cisplatin (ITP). These patients were also categorized into the low group (LG: n=30) or high group (HG: n=10). Fisher's exact test revealed no statistically significant differences between the two groups in terms of background patient characteristics (**Supplementary Table 1**).

Regarding the recurrent cases, median rCSS was 18.1 months (**Supplementary Fig. 1**). When comparing rCSS between the poCY HG and LG, the median rCSS in the HG was 11.2 months, which was significantly shorter than that in the LG (22.5 months) ($p < 0.001$) (**Supplementary Fig. 2**), with patients showing significantly longer survival ($p = 0.001$). When comparing rCSS by chemotherapy regimens, the median rCSS of the patients who received GC was 24.5 months, and that of those who received ITP was 20.6 months in the log-rank test, with no significant differences ($p = 0.587$) (**Supplementary Fig. 3**).

We also examined the poCY threshold of 3.8 ng/mL, which was calculated using the receiver operating characteristic (ROC) curve. The 2-year PFS rate in the HG was 37%, which was significantly lower than that in the LG (70%) ($p < 0.001$) (**Supplementary Fig. 4a**). Additionally, the 5-year CSS rate in the HG was 45%, which was significantly lower than that in the LG (84%) ($p < 0.001$) (**Supplementary Fig. 4b**). Multivariate analysis revealed that the poCY threshold of 3.8 ng/mL and LNI were prognostic factors for CSS and PFS (**Supplementary Table 2**).

Discussion

CK19 is an acid-type cytokeratin expressed in epithelial cells, and its soluble fragments are released during cell lysis. The CYFRA 21-1 assay, which uses monoclonal antibodies against BM19-21 and KS 19-1, can detect CK19 fragments in the blood. Elevated sCYFRA levels are associated with various malignancies and are prognostic predictors in non-small cell lung cancer[14]. CK19 is expressed in urothelial tumors[15,16]. In this study, we showed that elevated poCY levels significantly correlated with early disease progression in patients with UTUC who underwent RNU. Therefore, poCY may serve as a promising postoperative predictive biomarker in patients after surgery.

In this study, 117 patients who underwent RNU were enrolled, and 39 (35%) died during the median follow-up period of 34.0 (1-152) months. In this cohort, 65% of the

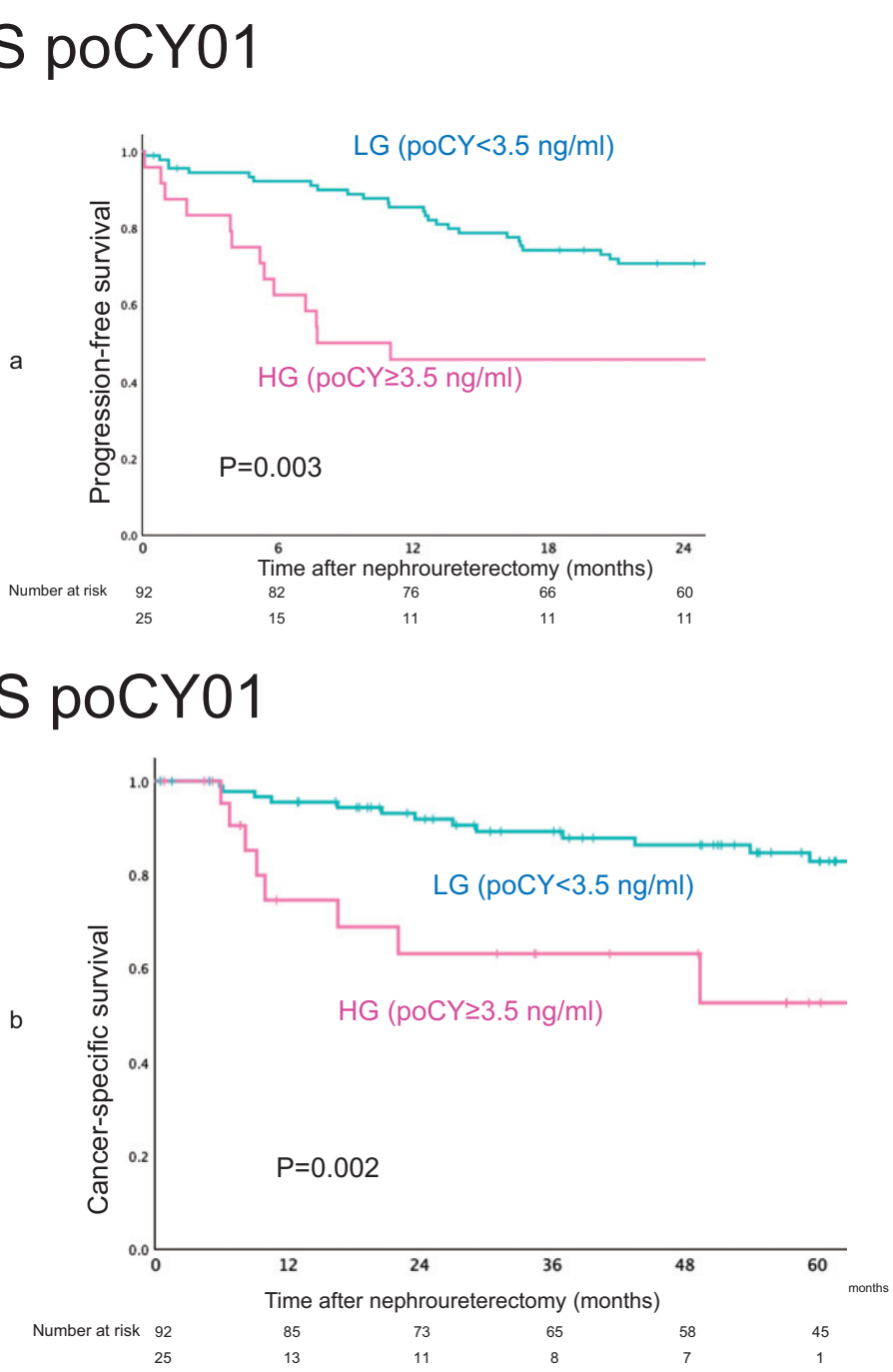

Fig. 3 Progression-free survival (PFS) (a) and cancer-specific survival (CSS) (b) rates in the high (postoperative serum level of the C-terminus of cytokeratin 19 [poCY] ≥ 3.5 ng/mL) and low (poCY<3.5 ng/mL) poCY groups. (a) Kaplan–Meier curve of PFS rate and months after radical nephroureterectomy of each group. In the log-rank test, the PFS rate of the low group was significantly longer than that of the high group (p = 0.003). (b) Kaplan–Meier curve of CSS rate and months after radical nephroureterectomy of each group. In the log-rank test, the CSS rate of the low group was significantly longer than that of the high group (p = 0.002).

patients had pT stage 2 or higher disease (pT ≥ 2), and the 2-year recurrence rate for these patients with pT stage ≥ 2 was 57%. These results are similar to those of the Peri-Operative chemotherapy versus sUrveillance in upper Tract urothelial cancer study (2-year PFS rate of patients with pT stage ≥ 2: 54%)[17], indicating that the population and treatment results in this study were typical and that the patients received standard care at our facility.

Elevated pretreatment sCYFRA levels are recognized as

Table 3 Univariate and multivariate Cox regression analyses for the prediction of PFS and CSS after treatment with radical nephroureterectomy (n = 117)

			2-year PFS						5-year CSS					
	n	%	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Sex			0.7	0.39–1.40	0.358				1.4	0.64–3.23	0.381			
Male	86	73.5												
Female	31	26.5												
Tumor Grade			2.0	1.07–3.72	0.029	1.8	0.81–3.86	0.153	9.8	1.2–19.7	0.028	3.6	0.42–30.6	0.238
G1, 2	48	41.0												
G3	69	59.0												
T stage			1.8	0.99–3.27	0.054				9.9	1.32–74.6	0.026	4.7	0.54–39.9	0.161
<pT2	41	35.0												
≥pT2	76	65.0												
Surgical method			1.1	0.59–2.12	0.740				6.8	2.34–20.0	0.090			
Open surgery with LND	30	25.6												
Laparoscopic surgery	87	74.4												
Primary tumor location			1.4	0.76–2.48	0.290				0.6	0.19–2.10	0.453			
Kidney	62	53.0												
Ureter	55	47.0												
Histological characteristics			1.8	0.81–3.98	0.152				3.6	0.92–11.4	0.078			
UC with subtype	14	12.0												
UC without subtype	103	88.0												
poCY			2.9	1.35–7.13	0.035	2.3	1.16–5.32	0.038	5.4	1.92–15.6	0.002	5.2	1.68-16.1	0.009
Low (<3.5 ng/mL)	92	78.6												
High (≥3.5 ng/mL)	25	21.4												
Pathological data on RNU														
Lymph node involvement			7.5	1.35–29.1	0.001	5.8	1.24–27.8	0.003	8.5	2.04–31.9	0.003	6.5	1.37–49.9	0.004
Negative	16	13.7												
Positive	14	12.0												
Lymphovascular invasion			2.3	1.14–4.81	0.020	1.3	0.96–3.22	0.056	2.8	1.10–7.31	0.058			
Negative	95	81.2												
Positive	22	18.8												
Resected margin			3.7	1.93–7.13	0.001	3.4	1.33–8.74	0.010	5.6	2.18–14.2	0.001	2.9	0.81–10.4	0.100
Negative	89	76.1												
Positive	28	23.9												

CI: confidence interval, CSS: cancer-specific survival, HR: hazard ratio, LND: lymph node dissection, PFS: progression-free survival, UC: urothelial carcinoma, poCY: postoperative serum level of the C-terminus of cytokeratin 19, RNU: radical nephroureterectomy

independent prognostic predictors[16], and sCYFRA has been associated with tumor invasion, metastasis, clinical response, and prognosis in bladder urothelial carcinoma (UC)[16,18,19]. However, the role of elevated postoperative CYFRA (poCY) levels in patients with upper tract urothelial carcinoma (UTUC) has not been widely discussed. Our study sheds light on this aspect, indicating that while poCY is statistically significant in multivariate models and continuous Cox regression analyses, its hazard ratios are modest, especially when compared to other pathological factors. This finding suggests that incremental increases in poCY levels may reflect subtle changes indicative of residual or micrometastatic disease, but their impact on clinical outcomes is less pronounced

Table 4 Background of patients with recurrence after radical nephroureterectomy (n=40)

n (%)	Total (n=40)	(%)
Sex		
Male	26	(65.0%)
female	14	(35.0%)
Median age, median (interquartile range), years	74	(52–75)
Grade		
G2	8	(20.0%)
G3	32	(80.0%)
T stage		
≤pT1	5	(12.5%)
pT2	10	(25.0%)
pT3	18	(45.0%)
pT4	7	(17.5%)
N stage		
pN0	4	(10.0%)
pN1	5	(12.5%)
pN2	5	(12.5%)
pNx (cN0)	26	(65.0%)
Primary tumor location		
Kidney	18	(45.0%)
Ureter	22	(55.0%)
Histological subtype		
No	33	(82.5%)
Yes	7	(17.5%)
Lymphovascular invasion		
Negative	30	(75.0%)
Positive	10	(25.0%)
Resected margin		
Negative	28	(70.0%)
Positive	12	(30.0%)
poCY		
<3.5 μg/mL	30	(75.0%)
≥3.5 μg/mL	10	(25.0%)

poCY: postoperative serum level of the C-terminus of cytokeratin 19

than that of other established pathological markers. Given these observations, continuous monitoring of poCY levels should be considered as an auxiliary tool, complementing traditional pathological assessments in the postoperative management of UTUC. This nuanced understanding supports the integration of poCY monitoring into clinical routines, albeit with a recognition of its relative limitations compared to more robust pathological indicators.

It is important to note that our study did not directly verify the cost implications of poCY monitoring. However, based on the general cost profiles of similar biomarkers and diagnostic tests, monitoring poCY could be more cost-effective compared to more expensive imaging, genetic, and molecular markers. Therefore, integrating poCY into routine clinical follow-up for UTUC could offer potential cost savings and improve resource allocation, aligning with the growing need for cost-efficient healthcare solutions.

Perioperative treatment for UTUC has several challenges. First, diagnosing UTUC is difficult. The upper urinary tract, particularly the ureter, is a relatively small organ, making it challenging to determine if a tumor within it is malignant. Additionally, determining if the tumor has invaded the muscular layer of the narrow ureter is extremely difficult, even with magnetic resonance imaging, which currently has the highest imaging resolution. Consequently, preoperative staging is complicated, leading to a clinical preference for postoperative chemotherapy after surgical treatment and patho-logical staging, which helps avoid overtreatment[20]. Moreover, postoperative chemo-therapy is preferred because NAC requires ureteroscopic biopsy, which may lead to tumor seeding in the lower urinary tract and increase the recurrence rate of lower urinary tract tumors[21]. Conducting prospective trials is difficult because UTUC is relatively rare, comprising only 5-10% of all UCs. This low prevalence makes it challenging to recruit sufficient patients for robust studies, resulting in small sample sizes and less statistically significant outcomes. Furthermore, patients present with varying stages and grades of disease, creating heterogeneity that complicates the standardization of treatment protocols and drawing generalizable conclusions across the entire patient population. Consequently, even if a prospective trial protocol is created, the number of patients meeting the criteria is usually insufficient. Many prospective trials have been conducted in the past, although most of them have been terminated prematurely due to enrollment issues, resulting in inconclusive outcomes.

Recently, increasing reports have shown that NAC yields good outcomes. As mentioned earlier, prospective trials are challenging to conduct for UC; therefore, no prospective trial has directly compared NAC to RNU alone. However, a recent multi-center phase II trial found that NAC in high-risk patients with UTUC provided a favorable pathological response, was well-tolerated with minimal surgery delays, and did not significantly increase perioperative complication risks[22]. A recent meta-analysis of 16 studies revealed that NAC could lead to a pathological complete response or downstaging and that NAC provides significant oncological benefits in CSS compared to RNU alone[23]. Additionally, a multicenter study in Japan found that the NAC group exhibited sig-

nificant improvements in OS compared to the ACT group[24]. NAC is primarily recommended for LTUC, with ACT suggested only for patients who cannot undergo NAC. However, UTUC is anatomically thinner and expected to invade and metastasize more quickly than LTUC, indicating that early treatment is even more crucial. Given that NAC improves OS in UTUC over ACT, it is likely to become the standard of care in UTUC treatment.

Although guidelines recommend adjuvant chemotherapy (ACT) for patients with stages ≥ ypT2 or ≥pT3 after RNU, the impact on overall survival (OS) is inconclusive[25]. Our study identified poCY level as a novel predictive marker for selecting ACT candidates, offering a more tailored approach beyond conventional pathology. However, this retrospective, single-center study with limited cases and a poCY cutoff of 3.5 ng/mL—based on bladder[13] and lung cancer[14] data—may have biases affecting the findings' generalizability for upper tract urothelial carcinoma (UTUC). Despite these limitations, the study provides valuable insights into poCY as a prognostic marker in UTUC, highlighting the need for further validation in larger, multi-center studies with prospective methodologies.

Conclusions

Our study provides valuable insights into the prognostic significance of elevated poCY levels in patients with UTUC who have undergone RNU. In addition to LNI and RM, poCY was identified as an independent predictor of oncological outcomes, including PFS and CSS. Clinicians can identify patients who may benefit from ACT independent of conventional pathological factors using poCY as a predictive biomarker. These findings can transform patient management and provide a more personalized and effective approach to treating patients with UTUC worldwide. However, further validation in larger cohorts and prospective studies is warranted to fully establish the clinical utility of poCY in the treatment of UTUC.

Conflict of Interest: Yukihiro Kondo received personal payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from the following companies: Astellas Pharma Inc., Nippon Kayaku Co., Ltd., and Bristol Meyers Squibb. Go Kimura received personal payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from the following companies: Ono Pharmaceutical, Bristol Myers Squibb, Merck Biopharma, Janssen Pharmaceutical, MSD, Eisai, Takeda, and Astellas. Yuki Endo received personal payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from the following companies: Astellas Pharma Inc., Nippon Kayaku Co., Ltd., Ono Pharmaceutical, and MSD.

Supplementary Information: Supplementary material is available in the online version at https://doi.org/10.1272/jnms.JNMS.2025_92-404.

References

1. Soria F, Shariat SF, Lerner SP, et al. Epidemiology, diagnosis, preoperative evaluation and prognostic assessment of upper-tract urothelial carcinoma (UTUC). World J Urol. 2017;35(3):379–87. doi: 10.1007/s00345-016-1928-x
2. Holmang S, Johansson SL. Urothelial carcinoma of the upper urinary tract: comparison between the WHO/ISUP 1998 consensus classification and WHO 1999 classification system. Urology. 2005;66(2):274–8. doi: 10.1016/j.urology.2005.03.011
3. Zigeuner R, Pummer K. Urothelial carcinoma of the upper urinary tract: surgical approach and prognostic factors. Eur Urol. 2008;53(4):720–31. doi: 10.1016/j.eururo.2008.01.006
4. Roupret M, Zigeuner R, Palou J, et al. European guidelines for the diagnosis and management of upper urinary tract urothelial cell carcinomas: 2011 update. Eur Urol. 2011;59(4):584–94. doi: 10.1016/j.eururo.2010.12.042
5. Favaretto RL, Shariat SF, Chade DC, et al. The effect of tumor location on prognosis in patients treated with radical nephroureterectomy at Memorial Sloan-Kettering Cancer Center. Eur Urol. 2010;58(4):574–80. doi: 10.1016/j.eururo.2010.07.003
6. Margulis V, Shariat SF, Matin SF, et al. Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. Cancer. 2009;115(6):1224–33. doi: 10.1002/cncr.24135
7. Fradet Y, Bellmunt J, Vaughn DJ, et al. Randomized phase III KEYNOTE-045 trial of pembrolizumab versus paclitaxel, docetaxel, or vinflunine in recurrent advanced urothelial cancer: results of >2 years of follow-up. Ann Oncol. 2019;30(6):970–6. doi: 10.1093/annonc/mdz127
8. Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med. 2020;383(13):1218–30. doi: 10.1056/NEJMoa2002788
9. Endo Y, Akatsuka J, Takeda H, et al. Real-world insights into efficacy and safety of enfortumab vedotin in Japanese patients with metastatic urothelial carcinoma: findings, considerations, and future directions. Curr Oncol. 2024;31(2):759–68. doi: 10.3390/curroncol31020056
10. Loriot Y, Necchi A, Park SH, et al. Erdafitinib in locally advanced or metastatic urothelial carcinoma. N Engl J Med. 2019;381(4):338–48. doi: 10.1056/NEJMoa1817323
11. Seisen T, Krasnow RE, Bellmunt J, et al. Effectiveness of adjuvant chemotherapy after radical nephroureterectomy for locally advanced and/or positive regional lymph node upper tract urothelial carcinoma. J Clin Oncol. 2017;35(8):852–60. doi: 10.1200/JCO.2016.69.4141
12. Necchi A, Lo Vullo S, Mariani L, et al. Adjuvant chemotherapy after radical nephroureterectomy does not im-

prove survival in patients with upper tract urothelial carcinoma: a joint study by the European Association of Urology-Young Academic Urologists and the Upper Tract Urothelial Carcinoma Collaboration. BJU Int. 2018;121(2):252–9. doi: 10.1111/bju.14020
13. Pujol JL, Molinier O, Ebert W, et al. CYFRA 21-1 is a prognostic determinant in non-small-cell lung cancer: results of a meta-analysis in 2063 patients. Br J Cancer. 2004;90(11):2097–105. doi: 10.1038/sj.bjc.6601851
14. Moll R, Franke WW, Schiller DL, Geiger B, Krepler R. The catalog of human cytokeratins: patterns of expression in normal epithelia, tumors and cultured cells. Cell. 1982;31(1):11–24. doi: 10.1016/0092-8674(82)90400-7
15. Suyama T, Nakajima K, Kanbe S, Tanaka N, Hara H, Ishii N. Prognostic significance of preoperative serum CYFRA 21-1 in patients with upper urinary tract urothelial carcinoma. Int J Urol. 2011;18(1):43–7. doi: 10.1111/j.1442-2042.2010.02671.x
16. Birtle A, Johnson M, Chester J, et al. Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. Lancet. 2020;395(10232):1268–77. doi: 10.1016/S0140-6736(20)30415-3
17. Andreadis C, Touloupidis S, Galaktidou G, Kortsaris AH, Boutis A, Mouratidou D. Serum CYFRA 21-1 in patients with invasive bladder cancer and its relevance as a tumor marker during chemotherapy. J Urol. 2005;174(5):1771–5; discussion 1775–6. doi: 10.1097/01.ju.0000176742.53556.25
18. Senga Y, Kimura G, Hattori T, Yoshida K. Clinical evaluation of soluble cytokeratin 19 fragments (CYFRA 21-1) in serum and urine of patients with bladder cancer. Urology. 1996;48(5):703–10. doi: 10.1016/S0090-4295(96)00253-1
19. Kolawa A, D'Souza A, Tulpule V. Overview, diagnosis, and perioperative systemic therapy of upper tract urothelial carcinoma. Cancers (Basel). 2023;15(19):4813. doi: 10.3390/cancers15194813
20. Lee JK, Kim KB, Park YH, et al. Correlation between the timing of diagnostic ureteroscopy and intravesical recurrence in upper tract urothelial cancer. Clin Genitourin Cancer. 2016;14(1):e37–41. doi: 10.1016/j.clgc.2015.07.008
21. Coleman JA, Yip W, Wong NC, et al. Multicenter phase II clinical trial of gemcitabine and cisplatin as neoadjuvant chemotherapy for patients with high-grade upper tract urothelial carcinoma. J Clin Oncol. 2023;41(8):1618–25. doi: 10.1200/JCO.22.00763
22. Leow JJ, Chong YL, Chang SL, Valderrama BP, Powles T, Bellmunt J. Neoadjuvant and adjuvant chemotherapy for upper tract urothelial carcinoma: a 2020 systematic review and meta-analysis, and future perspectives on systemic therapy. Eur Urol. 2021;79(5):635–54. doi: 10.1016/j.eururo.2020.07.003
23. Takahashi K, Urabe F, Suhara Y, et al. Comparison of neoadjuvant and adjuvant chemotherapy for upper tract urothelial carcinoma in real-world practice: a multicenter retrospective study. Jpn J Clin Oncol. 2023;53(12):1208–14. Erratum in: Jpn J Clin Oncol. 2023 Dec 7;53(12):1217. doi: 10.1093/jjco/hyad118
24. Bolenz C, Fernandez MI, Trojan L, et al. Lymphovascular invasion and pathologic tumor stage are significant outcome predictors for patients with upper tract urothelial carcinoma. Urology. 2008;72(2):364–9. doi: 10.1016/j.urology.2008.04.032
25. Morita T, Kikuchi T, Hashimoto S, Kobayashi Y, Tokue A. Cytokeratin-19 fragment (CYFRA 21-1) in bladder cancer. Eur Urol. 1997;32(2):237–44.

(Received, November 8, 2024)
(Accepted, March 26, 2025)