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Prognostic impact of perirenal fat stranding on oncologic outcomes in ureteral urothelial carcinoma

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Purpose: Perirenal fat stranding (PRFS) is defined as linear areas of soft-tissue attenuation in the perirenal space that can result from ureteral obstruction. We analyzed the prognostic impact of PRFS on outcomes in patients with ureteral urothelial carcinoma (UC).

Materials and Methods: Overall, 126 patients evaluated preoperatively by computerized tomography (CT) scan and diagnosed with ureteral UC following nephroureterectomy between January 2001 and May 2018 were included. We analyzed associations between oncologic outcomes and secondary signs such as hydronephrosis and PRFS.

Results: Overall, 68 patients (54.0%) showed PRFS on preoperative CT scans. The patients' mean age was 66.33±9.49 years. A high pT stage (≥T3) was seen in 47 patients (37.3%) and high-grade tumors were seen in 90 patients (71.4%). Lymphovascular invasion (LVI) was seen in 15 patients (11.9%), and 5 (4.0%) were at the pN1 stage. Multivariate Cox analysis showed that cT stage≥3, PRFS, pT stage≥3, tumor grade, LVI, and pN1 stage were independent prognostic factors of recurrence-free survival (RFS) and cancer-specific survival (CSS) (all $p<0.05$).

Conclusions: PRFS was found to be an independent prognostic factor for RFS and CSS. PRFS is easily detectable in preoperative CT imaging and may be useful for improving the prediction of oncologic outcomes of ureteral UC. Therefore, PRFS along with other important preoperative CT findings can help urologists give preoperative advice to patients with ureteral UC before surgical management.

Keywords: Carcinoma; Survival; Ureter; Urothelium

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INTRODUCTION

Upper tract urothelial carcinoma (UTUC) is defined as a malignancy that arises from the renal collecting system or ureter; however, the majority of lesions develop in the renal pelvis. UTUC is a relatively rare neoplasm with a prevalence of 5% to 10% among all those with urothelial carcinoma (UC) [1]. However, the incidence of ureteral UC has been rising in the past 50 years and is estimated to occur in 25% to 33% of patients with UTUC [2,3].

Several prognostic factors for ureteral UC have been reported, including pathologic TNM stage, tumor grade, and tumor location. Although comparative studies of oncologic outcomes for renal pelvic UC versus ureteral UC have been performed, the results have been conflicting. A few studies have suggested that no differences in oncologic outcomes exist between renal pelvic UC and ureteral UC [4,5]; however, the majority of studies have reported that ureteral UC has a worse prognosis [6-10].

Because of diagnostic difficulties, ureteral UC often has a rapid progression and poor prognosis [11,12]. Therefore, it is important for urologists to obtain an accurate diagnosis and subsequently implement immediate medical or surgical treatment. In particular, a meticulous understanding of the various signs identified on preoperative computed tomography (CT) imaging can help surgeons in counseling patients with ureteral UC. Especially, perirenal fat stranding (PRFS), defined as linear or curvilinear soft-tissue attenuation in the perirenal area, has been previously investigated as a secondary sign of ureteral obstruction on CT findings in diverse renal diseases by numerous studies [11,13]. We hypothesized that PRFS could develop by extravasated urine or lymphatics caused by ureteral obstruction, which could worsen the prognosis of ureteral UC.

To our knowledge, articles that focus on secondary signs identified on preoperative CT scanning are limited. Therefore, in this study, we aimed to evaluate the prognostic impact of secondary signs of upper urinary obstruction, especially PRFS, on the oncologic outcomes of patients with ureteral UC who underwent radical nephroureterectomy.

MATERIALS AND METHODS

1. Study population

This study was approved by the Institutional Review Board of Kyungpook National University, School of Medicine, Daegu, Korea (approval number: KNUH 2020-03-014). The board exempted informed consent owing to the retrospective nature of this research.

We retrospectively reviewed the charts of 410 consecutive patients with UTUC who underwent radical nephroureterectomy at our institution between January 2001 and May 2018. No patients had distant metastasis at the time of radical nephroureterectomy. Fig. 1 shows the flowchart diagram of the inclusion and exclusion criteria. Patients were excluded if they had renal pelvic UC only or had both renal pelvic and ureteral UC. Patients were also excluded if they had bilateral UTUC, had previous or concurrent bladder

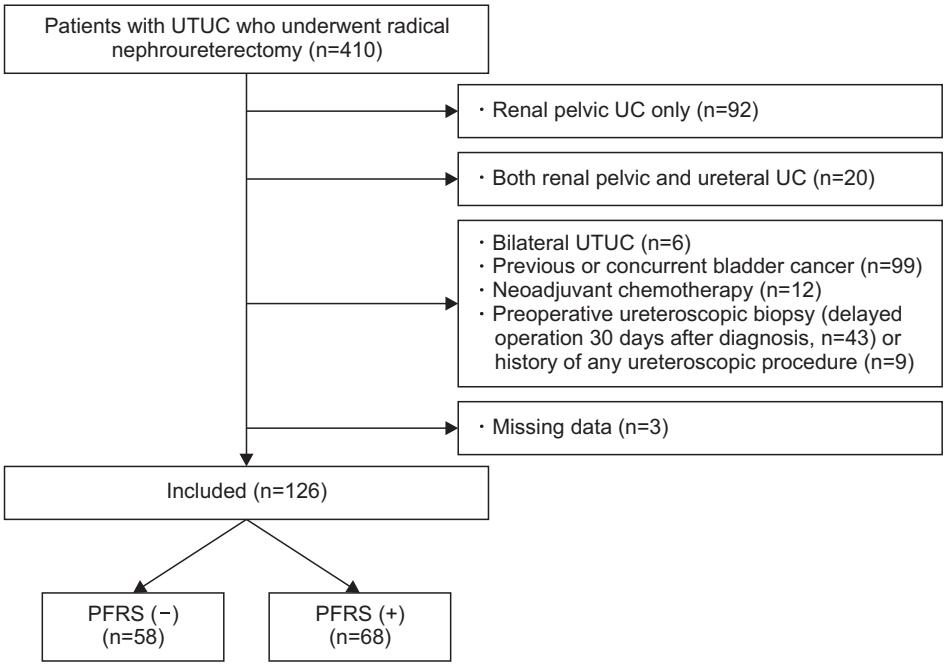

Fig. 1. Flowchart diagram. UTUC, upper tract urothelial carcinoma; UC, urothelial carcinoma; PRFS, perirenal fat stranding.

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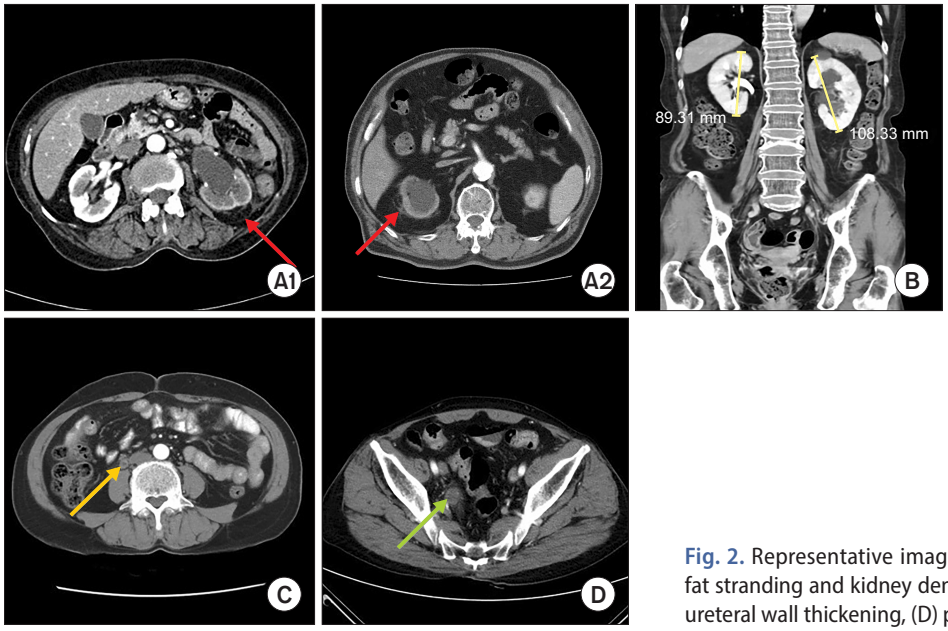

Fig. 2. Representative images of secondary signs. (A1, A2) Perirenal fat stranding and kidney density difference, (B) renal enlargement, (C) ureteral wall thickening, (D) periureteral fat stranding.

cancer, received neoadjuvant chemotherapy, had a history of preoperative ureteroscopic biopsy before nephroureterectomy (delayed operation 30 days after diagnosis), or had a history of any ureteroscopic procedures due to ureter strictures. After the application of these exclusion criteria, 126 patients with ureteral UC only were included. Patients were followed up for a minimum of 24 months and all underwent radical nephroureterectomy within 4 weeks of their clinical diagnosis of ureteral UC [14,15]. The serum creatinine level of all patients was within the normal range.

2. Definition

The classification of hydronephrosis grading was done based on the Society for Fetal Urology guidelines [16]. A preoperative CT scan was reviewed independently by a single specialized uroradiologist with no knowledge of the clinical information of the patients (Fig. 2). All patients were reevaluated by CT scan at least 1 week before surgery.

PRFS or periureteral fat stranding (PUFS) was defined as increased density or stranding in the surrounding perirenal or periureteral adipose tissue as a result of obstruction secondary to ureteral UC [17]. Renal enlargement was defined as an increase in thickness of the renal parenchyma or an increase in the length of the kidney due to obstruction [18]. For enlarged kidneys, the parenchymal thickness of each in the mid-zone planes and the length of the kidneys were measured, and asymmetrical increases were noted. The difference in kidney density was evaluated and identified if an asymmetric density difference of 5 Hounsfield units (HU) or greater existed between tumor-affected and unaffected kidneys [19,20]. Cortical thinning was defined as a renal parenchymal thickness less than 12 mm [21]. Ureteral wall thickening was defined as a thickened ureteral wall of more than 2 mm with noticeable distinction compared with that of the ipsilateral ureteral wall [22].

In the case of multiple UC lesions, the tumor locations were determined by first identifying the location of the largest UC lesion according to pathologic reports. Cancer stage was determined by using the American Joint Committee on Cancer staging system and histological grade was determined by using the 2004 World Health Organization classification system.

The local recurrence-free survival (RFS) interval was defined as the time to intravesical recurrence (recurrence of ureteral UC within the bladder) or extravesical recurrence (surgical bed or regional lymph node enlargement greater than 1 cm on postoperative imaging studies). The distant RFS interval was defined as the time to distant metastasis to a solid organ or beyond the regional lymph node. The cancer-specific survival (CSS) interval was defined as the time between the surgery date and cancer-specific death.

3. Surgical technique and follow-up regimen

Radical nephroureterectomy was performed via the open retroperitoneal approach or laparoscopic transperitoneal approach. Subsequently, bladder cuff excision was performed by using the extravesical approach via the Gibson incision; a lymphadenectomy was performed if lymphadenopathy was suspected by the preoperative CT scan or was observed during the operation. The site and the extent of lymphad-

enectomy were determined on the basis of tumor location. The majority of patients (46 cases) with non-organ-confined disease underwent platinum-based adjuvant chemotherapy. The operation time was calculated as the time from initial incision to closure. The follow-up regimen included cystoscopy, urine cytology, chest X-ray, and CT scanning. Cystoscopy and urine cytology were performed at 3, 6, and 12 months postoperatively, then every 6 months until 2 years after the operation, and yearly thereafter. Imaging analyses, including chest X-ray and CT scanning, were performed at 3, 6, and 12 months postoperatively, then every 6 months from 1 to 5 years, and annually thereafter.

4. Statistical analysis

Continuous variables were compared by a Student's t-test. Comparisons of noncontinuous variables were performed by chi-square or Fisher's exact tests. The co-variables included in the analysis were age, sex, body mass index, hospital stay, follow-up period, surgical information (open versus laparoscopic, performance of bladder cuff excision, operative time), preoperative clinical data from imaging (laterality, hydronephrosis, PRFS, renal enlargement, kidney density difference, cortical thinning, ureteral wall thickening, PUFS, radiologic tumor location, radiologic tumor size, tumor multiplicity, cTN stage), and pathologic outcomes (tumor location, maximal tumor size, concomitant carcinoma *in situ* [CIS], multifocal tumor, pTN stage, tumor grade, lymphovascular invasion [LVI], and margin status).

Kaplan-Meier curve analysis was used to assess rates of RFS and CSS. Univariate and multivariate Cox proportional hazard regression models were used to calculate the hazard ratio (HR) of each prognostic variable. Statistical analysis was performed by using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA), and $p<0.05$ was considered statistically significant.

Table 1. The characteristics of patients according to presence of PRFS

Variable	PRFS (-) (n=58)	PRFS (+) (n=68)	p-value
Age (y)	64.95±10.13	67.50±8.81	0.133
Sex, female/male	19 (32.8)/39 (67.2)	22 (32.4)/46 (67.6)	0.961
Body mass index (kg/m^2)	23.80±3.38	23.86±3.53	0.924
Laterality, left/right	25 (43.1)/33 (56.9)	39 (57.4)/29 (42.6)	0.111
Hydronephrosis, 0, 1, 2/3, 4	29 (50.0)/29 (50.0)	16 (23.5)/52 (76.5)	0.002
Renal enlargement, no/yes	47 (81.0)/11 (19.0)	49 (72.1)/19 (27.9)	0.238
Kidney density difference, no/yes	30 (51.7)/28 (48.3)	17 (25.0)/51 (75.0)	0.002
Cortical thinning, no/yes	42 (72.4)/16 (27.6)	38 (55.9)/30 (44.1)	0.055
Ureteral wall thickening, no/yes	26 (44.8)/32 (55.2)	13 (19.1)/55 (80.9)	0.002
Periureteral fat stranding, no/yes	42 (72.4)/16 (27.6)	19 (27.9)/49 (72.1)	<0.001
Radiologic tumor location, lower/mid or upper	31 (53.4)/27 (46.6)	43 (63.2)/25 (36.8)	0.266
Radiologic tumor size (cm)	3.32±1.94	4.00±2.73	0.118
Tumor multiplicity, no/yes	49 (84.5)/9 (15.5)	48 (70.6)/20 (29.4)	0.065
cT stage, T1 or 2/≥T3	40 (69.0)/18 (31.0)	37 (54.4)/31 (45.6)	0.095
cN stage, N0/N1	58 (100.0)/0 (0.0)	65 (95.6)/3 (4.4)	0.105
Tumor location, lower/non-lower	31 (53.4)/27 (46.6)	43 (63.2)/25 (36.8)	0.266
Maximal tumor size (cm)	3.28±1.93	3.96±2.80	0.122
Concomitant CIS, no/yes	54 (93.1)/4 (6.9)	60 (88.2)/8 (11.8)	0.353
Multifocal tumor, no/yes	48 (82.8)/10 (17.2)	46 (67.6)/22 (32.4)	0.052
pT stage, organ confined/non-organ confined	41 (70.7)/17 (29.3)	38 (55.9)/30 (44.1)	0.087
Tumor grade, low/high	23 (39.7)/35 (60.3)	13 (19.1)/55 (80.9)	0.011
Lymphovascular invasion, no/yes	55 (94.8)/3 (5.2)	56 (82.4)/12 (17.6)	0.031
N stage, Nx or 0/N1	58 (100.0)/0 (0.0)	63 (92.6)/5 (7.4)	0.061[a]
Margin positive, no/yes	57 (98.3)/1 (1.7)	64 (94.1)/4 (5.9)	0.373[a]
Local or distant recurrence, no/yes	49 (84.5)/9 (15.5)	45 (66.2)/23 (33.8)	0.019
Cancer-specific death	7 (12.1)	23 (33.8)	0.004
Adjuvant chemotherapy	20 (34.5)	26 (38.2)	0.663

Values are presented as mean±standard deviation or number (%).
PRFS, perirenal fat stranding; CIS, carcinoma *in situ*.
[a]:Fisher's exact test.

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RESULTS

The patients' mean age was 66.33±9.49 years. Males accounted for 67.5% (85/126) of the patient population. The mean follow-up period was 50.40±36.29 months. The laparoscopic approach was performed in 114 patients (90.5%) and bladder cuff excisions were performed in 120 patients (95.2%). The mean operative time was 4.89±1.15 hours. Hydronephrosis was observed 114 patients (90.5%) on the preoperative CT scan. The number of patients with PRFS and PUFS was 68 (54.0%) and 65 (51.6%), respectively. Lower ureteral UC was observed in 58.7% (74/126). Radiologic tumor size was 3.69±2.41 cm. Multifocal tumors were observed in 29 patients (23.0%). cT stage ≥3 was found in 49 patients (38.9%) and cN1 in 3 (2.4%), respectively. Concomitant CIS was identified in 12 patients (9.5%). High-grade ureteral UC was observed in 90 patients (71.4%) and LVI was seen in 15 patients (11.9%). Lymph node involvement and positive margins were identified in 5 patients (4.0%) each. Local or distant recurrence was experienced by 32 patients (25.4%). Adjuvant chemotherapy was received by 46 patients and the rate of cancer-specific death was 23.8%.

The characteristics of patients according to the presence of PRFS are listed in Table 1. Signs of hydronephrosis (50.0% vs. 76.5%), kidney density difference (48.3% vs. 75.0%), ureteral wall thickening (55.2% vs. 80.9%), and PUFS (27.6% vs. 72.1%) were significantly higher in patients with PRFS (all p<0.05). High-grade tumors (60.3% vs. 80.9%) and LVI (5.2% vs. 17.6%) were also significantly more prevalent in patients with PRFS (all p<0.05). Furthermore, local or distant recurrence (15.5% vs. 33.8%) and cancer-specific death (12.1% vs. 33.8%) were significantly higher in patients with PRFS (all p<0.05).

Table 2 contains the univariate and multivariate analysis of local or distant RFS and CSS for patients with ureteral UC according to preoperative variables. PRFS was an independent prognostic factor for RFS (HR, 1.974; 95% confidence interval [CI], 0.908–4.289; p=0.036) and CSS (HR, 2.533; 95% CI, 1.079–5.947; p=0.033). cT stage was also an independent prognostic factor. Furthermore, there were significant differences in RFS and CSS according to PRFS in the Kaplan-Meier curve analysis (all p<0.05) (Fig. 3). Table 3 contains the univariate and multivariate analysis of local and distant RFS and CSS according to pathologic variables. pTN stage, tumor grade, and LVI were independent prognostic factors of RFS and CSS (all p<0.05).

Table 2. Univariate and multivariate analysis of local/distant recurrence-free survival and cancer-specific survival for patients with ureteral urothelial carcinoma according to preoperative variables

Variable	Local/distant recurrence-free survival			Cancer-specific survival		
	p-value		HR (95% CI)	p-value		HR (95% CI)
	Univariate	Multivariate		Univariate	Multivariate	
Age (y)	0.033	0.058	1.044 (0.999–1.092)	0.004	0.012	1.066 (1.014–1.121)
Sex, female vs. male	0.258	-	-	0.580	-	-
Radiologic tumor location, mid or upper vs. low	0.616	-	-	0.557	-	-
Radiologic tumor size	0.834	-	-	0.663	-	-
Tumor multiplicity, no vs. yes	0.427	-	-	0.586	-	-
cT stage, T1 or 2 vs. ≥T3	<0.001	0.001	5.328 (2.385–11.904)	<0.001	0.001	5.322 (2.267–12.497)
cN stage, N0 vs. N1	0.096	-	-	0.078	-	-
Body mass index (kg/m^2)	0.688	-	-	0.121	-	-
Hydronephrosis, no vs. yes	0.034	0.973	Unavailable	0.068	-	-
Perirenal fat stranding, no vs. yes	0.019	0.036	1.974 (0.908–4.289)	0.004	0.033	2.533 (1.079–5.947)
Periureteral fat stranding, no vs. yes	0.307	-	-	0.291	-	-

HR, hazard ratio; CI, confidence interval.

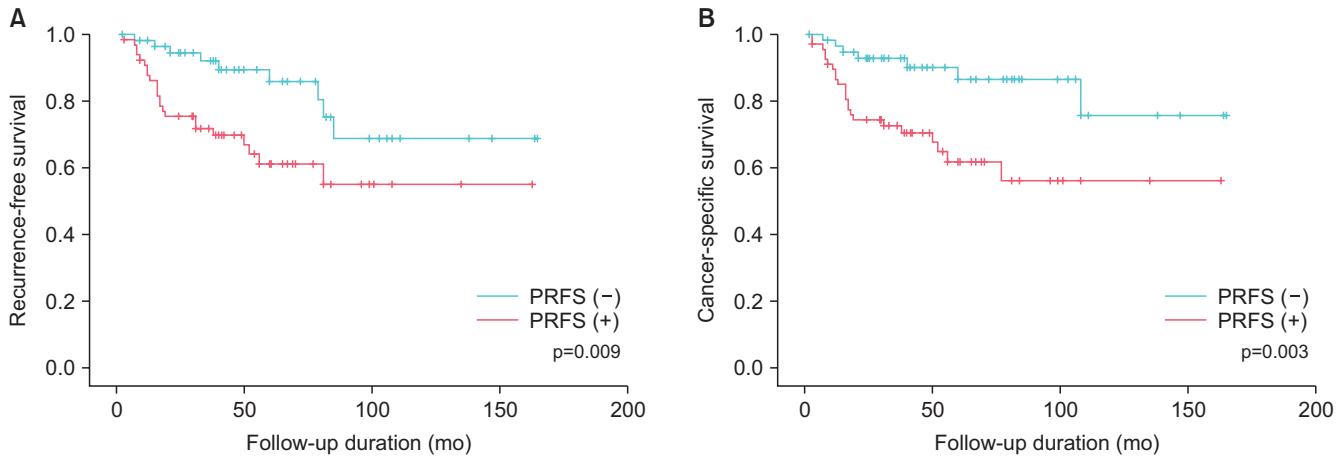

Fig. 3. Probability estimates of RFS (A) and CSS (B) rates in all patients stratified by perirenal fat stranding using Kaplan-Meier curve analysis. RFS, recurrence-free survival; CSS, cancer-specific survival.

DISCUSSION

In this study, we found that both perioperative clinical and pathologic factors contributed to the oncologic outcomes of UTUC. In 2014, our center evaluated the impact of surgical wait time on oncologic outcomes in those with UTUC [15]. A subgroup analysis of the 80 patients with only ureteral UC showed that RFS and CSS were significantly higher in the early surgical wait time group (within 30 days). Furthermore, the multivariate analysis indicated that a surgical wait time over 1 month was an independent prognostic factor of RFS and CSS for those with ureteral UC (p=0.04 and p<0.001). In the present study, therefore, to accurately assess the outcomes of RFS and CSS, we excluded the patients with UC who endured longer surgical wait times that may have affected the oncologic outcomes. We included only patients with ureteral UC who underwent radical nephroureterectomy within 4 weeks of their diagnosis.

Recently, with the remarkable technological advancements in radiology, CT imaging has greatly contributed to the diagnosis and staging of UTUC [23]. CT urography is the most optimized noninvasive imaging technique for evaluating UTUC. Hydronephrosis on a CT scan is the most frequent finding in those with ureteral UC. The condition develops as a result of the small diameter of the ureteral lumen. Brien et al. [24] suggested that patients with hydronephrosis identified on a preoperative CT scan are at risk for non-organ-confined disease and should be considered for more aggressive treatments. In 2007, Cho et al. [25] evaluated the association between hydronephrosis grade and prognosis of patients with ureteral UC. Overall, 104 patients who underwent radical nephroureterectomy following a diagnosis of ureteral UC were analyzed retrospectively. Hydronephrosis grade was associated with pT stage (p<0.001) and had a significant impact on CSS (p=0.008). Another study by Luo et al. [26] demonstrated that the severity of hydronephrosis correlated with tumor invasiveness and bladder recurrence of ureteral UC. Hydronephrosis grade >2 was independently associated with non-organ-confined ureteral UC (p=0.003) and was an independent factor for predicting bladder recurrence (p=0.021). Consistent with these results, Ng et al. [27] concluded that preoperative hydronephrosis on axial CT scans is associated with aggressive disease and can predict advanced pT stage for those with UTUC. However, these findings are not consistent with those of our study. We found that the presence or grade of hydronephrosis was not a significant factor according to the multivariate analysis of local or distant RFS and CSS.

Despite the publication of abundant studies indicating associations between hydronephrosis and UTUC, literature concerning PRFS as a secondary sign of ureteral UC is not common. Most of the current research regarding secondary signs on CT scans involves the identification of ureteral stones [28-30]. PRFS is defined as linear or curvilinear soft-tissue attenuation without vascular connection distributed in the perirenal space [13]. The kidneys are suspended in the perirenal space by the reticular bridging septa connecting the renal capsule to the Gerota's fascia. When any pathologic process occurs in the perirenal area along the bridging septa, PRFS is seen on CT images. PRFS is thought to be associated with a wide spectrum of diseases and conditions including acute ureteral obstruction, pyelonephritis, and acute pancreatitis. The development of PRFS due to acute or chronic ureteral obstruction can be explained by two possible mechanisms. First, when the ureter is obstructed, the increased renal pelvic pressure results in a microscopic

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Table 3. Univariate and multivariate analysis of local/distant recurrence-free survival and cancer-specific survival for patients with ureteral urothelial carcinoma according to pathologic variables

Variable	Local/distant recurrence-free survival			Cancer-specific survival		
	p-value		HR (95% CI)	p-value		HR (95% CI)
	Univariate	Multivariate		Univariate	Multivariate	
Tumor location, mid or upper vs. low	0.430	-	-	0.226	-	-
Maximal tumor size (cm)	0.790	-	-	0.671	-	-
CIS, no vs. yes	0.974	-	-	0.919	-	-
Multifocal tumor, no vs. yes	0.378	-	-	0.507	-	-
pT stage, OC (a, 1, 2) vs. non OC (≥ 3)	<0.001	<0.001	4.622 (2.030–10.527)	<0.001	0.001	4.366 (1.872–10.182)
Tumor grade, low vs. high	0.020	0.037	1.400 (0.395–4.963)	0.010	0.032	1.967 (0.501–7.721)
LVI, no vs. yes	<0.001	0.001	4.019 (1.845–8.753)	<0.001	0.008	3.090 (1.347–7.093)
pN stage, Nx or 0 vs. N1	0.016	0.026	4.938 (1.583–15.404)	0.010	0.039	3.039 (0.984–9.384)
Positive surgical margin, no vs. yes	0.444	-	-	0.386	-	-

HR, hazard ratio; CI, confidence interval; -, not available; CIS, carcinoma *in situ*; OC, organ confined; LVI, lymphovascular invasion.

rupture at the calyceal fornix, which is the area of least resistance; subsequently, pyelosinus backflow of urine may occur. Extravasated urine from the renal hilum can enter the perirenal space and infiltrate along the bridging septa. The second mechanism involves bridging septa thickening that may result from lymphatic dilation and subsequent extravasation. If the elevated renal pelvic pressure compresses the hilar lymphatic chains, the lymph drains backward to the perinephric lymphatics, which run along the fibrous septa of the perirenal space. On the basis of these explanations, we hypothesized that PRFS on CT scans could be associated with poor prognosis of ureteral UC.

Most of the secondary signs are caused by ureteral obstruction; however, not all of these secondary signs accurately reflect the degree of ureteral obstruction. We presumed that PRFS accurately reflects the pathophysiologic condition associated with the disruption in balance between pressure in the collecting system and ureteral wall resistance. Thus, PRFS may be a secondary sign that more accurately reflects the degree of ureteral obstruction in the case of large ureteral tumors. Following our analysis, PRFS was found to be an independent factor for RFS and CSS, which may be explained as follows. First, in cases of rapidly growing ureteral UC, PRFS due to acute or subacute ureteral obstruction may occur suddenly. Therefore, we propose that PRFS more accurately reflects the growth and progression of ureteral UC than hydronephrosis. Second, in cases of severe obstruction, we hypothesized that tumor cell spreading may occur through extravasation of urine or lymphatics; thus, PRFS likely reflects the severity of ureteral obstruction. Considering these two hypothesis, to the best our best knowledge, this study is the first to identify the association between oncologic outcomes of ureteral UC and PRFS as a secondary sign on CT scan. Furthermore, some patients with severe hydronephrosis did not show any PRFS; conversely, some patients with severe PRFS did not show any hydronephrosis. In this respect, we presumed that these factors may be independent of one other. In other words, the various secondary signs we used for the analysis are the results of obstruction due to ureteral UC. We suggest that the mechanisms by which these secondary signs occur are different. Because the mechanisms differ, it was expected that the effects of each secondary sign on oncologic outcomes will differ, and the results were the same.

However, several limitations of our study should be considered. First, it was based on a retrospective analysis of patient records from a single institution; retrospective studies always introduce sampling bias. Strict exclusion criteria may have limited the generalizability of the results and

may have provided incomplete observations of the ureteral UC spectrum. Second, the number of patients was small and more than one surgeon performed the procedures, which adds heterogeneity to the analysis. Also, we have to consider that in early 2000, surgical techniques and methods were still slightly underdeveloped compared with those available today. Furthermore, we did not have information on the time interval from initial symptom presentation to referral time and evaluation. Although all patients underwent nephroureterectomy within 4 weeks of initial diagnosis, selection bias regarding the timing of surgery was unavoidable because decisions were made following consultation between patients and surgeons. In addition, routine lymphadenectomy was not performed in those with muscle-invasive ureteral UC but rather was performed in selected patients. Furthermore, to achieve the scientific rationale of this study, pathologic examination of PRFS or imaging study concerning how signs of PRFS change when patients with PRFS finish chemotherapy after nephroureterectomy should be performed in the near future. These aspects, along with the retrospective nature of our study, introduce a significant likelihood of bias; therefore, the conclusions should be interpreted with caution. In the future, further large-scale, population-based, multi-institutional prospective studies to assess factors that may influence the outcomes of those with ureteral UC should be considered.

CONCLUSIONS

PRFS on preoperative CT scan in patients with ureteral UC was found to be an independent prognostic factor of RFS and CSS. PRFS is easily detectable in preoperative CT scans and may be useful for improving the prediction of oncologic outcomes of ureteral UC. Therefore, PRFS along with other important preoperative CT findings can help urologists give preoperative advice to patients with ureteral UC before surgical management.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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