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상부요로상피암에서 신장보존수술: 요관암에 대한 수술적 치료의 패러다임 변화

Kidney Sparing Surgery in Upper Tract Urothelial Carcinoma: Paradigm Change in Surgical Treatment for Ureter Cancer

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ABSTRACT

Introduction

Ureter cancer presents a unique benefit with a range of kidney-sparing surgical options, contrasting with renal pelvis cancer. Current guidelines lack a nuanced consideration of renal function, focusing predominantly on risk-based disease management and without distinction between renal pelvis and ureter cancers. In this study, I aimed to demonstrate appropriate management for ureter cancer, especially in terms of kidney sparing surgery (KSS), by comparing the oncologic outcomes and renal function between patients who underwent radical nephroureterectomy (RNU) and those who underwent KSS.

Materials and Methods

Between 2011 and 2019, 708 upper tract urothelial carcinoma (UTUC) patients underwent RNU (N = 646) or KSS (N = 62) at Asan Medical Center. Retrospective analysis highlighted tumor unifocality as a significant prognostic factor in non-invasive (≤pT1) UTUC. Subgroup analysis focused on unifocal ureter cancer (UUC) to analyze renal function and oncological outcomes between RNU and KSS. Ultimately, I aimed to identify potential KSS candidates among patients with ureter cancer who initially underwent RNU.

Results

No significant differences were observed in intravesical recurrence-free survival (IRFS), metastasis-free survival (MFS), cancer-specific survival (CSS), or overall survival (OS)

between RNU and KSS groups in UTUC.

In non-invasive (≤pT1) UTUC subgroup, tumor multifocality emerged as an independent risk factor for CSS (HR = 2.221, 95% CI: 1.231-4.010, P = 0.008). In non-invasive (≤pT1) pure ureter cancer (PUC) subgroup, tumor multifocality was also identified as a significant risk factor for CSS (HR = 2.627, 95% CI: 1.305-5.980, P = 0.019).

In the UUC subgroup, the average change in estimated glomerular filtration rate (eGFR) decreased in the RNU group (-11.2 ± 17.8 mL/min/1.73 m^2), while in the KSS group, it showed a slight increase (3.1 ± 7.9 mL/min/1.73 m^2; P < 0.000). After 1:1 propensity score matching of the UUC subgroup into RNU (N = 50) and KSS (N = 50) groups, there was no significant difference in survival rates between the two surgical methods.

Among the patients with PUC who underwent RNU (N = 292), the number of patients with UUC, excluding those with a single kidney (N = 2), CKD stage 4 or below (N = 15), contralateral renal function (CRF) ≥50 mL/min/1.73 m^2 and ipsilateral renal function (IRF) <30 mL/min/1.73 m^2 (N = 72), was 152 (52.1%). There were 28 patients with CRF ≥50 mL/min/1.73 m^2 and IRF ≥30 mL/min/1.73 m^2, 59 patients with CRF <50 mL/min/1.73 m^2 and IRF <30 mL/min/1.73 m^2, and 35 patients with CRF <50 mL/min/1.73 m^2 and IRF ≥30 mL/min/1.73 m^2.

Conclusions

For ureter cancer patients with single kidneys, CKD stage 4 or below, bilateral tumors, or high surgical morbidity, KSS is the initial recommendation. When CRF is ≥50 mL/min/1.73 m^2 and IRF is <30 mL/min/1.73 m^2, RNU is proactive. If CRF is <50 mL/min/1.73 m^2 and IRF is ≥30 mL/min/1.73 m^2, KSS may be recommended to enhance

the likelihood of adjuvant chemotherapy. The decision between RNU and KSS should take into consideration tumor characteristics, clinical staging, and patient preferences for kidney preservation.

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INTRODUCTION

Epidemiology of UTUC

Upper tract urothelial carcinoma (UTUC) constitutes 5–10% of urothelial tumors affecting the renal pelvis and ureter [1]. UTUC encompasses malignancies arising from the urothelial lining of the urinary tract [2]. Emerging diagnostic methods, advanced imaging, and improved endoscopic techniques contribute to the increased incidence of UTUC [3].

The average age at diagnosis has increased from 68 to 73 years over the past thirty years [4]. UTUC exhibits a higher prevalence in men, with a male-to-female ratio of 2:1 [5]. This ratio is more balanced compared to the 4:1 gender disparity seen in urothelial carcinoma of the bladder [6]. Interestingly, while females tend to present with invasive tumor stages and poorer prognosis in urothelial carcinoma of the bladder, this pattern is not observed in UTUC [7].

Data from recent radical nephroureterectomy (RNU) series reveal an apparent uptick in aggressive disease, with 60% locally advanced, 70% high-grade tumors, and 7% metastatic cases [8]. Multifocal tumors occur in approximately 25% of new UTUC cases, and 20% present with concomitant urothelial carcinoma of the bladder [9]. Concomitant carcinoma in situ (CIS) of the upper tract varies between 11–36% [10].

The renal pelvis is a central, hollow structure within each kidney. In contrast, the ureters are slender, tube-like structures responsible for linking the kidneys to the bladder. From an anatomical perspective, the ureter can be delineated into three distinctive segments. The proximal ureter, extending from the ureteropelvic junction to the superior margin of the sacrum. The mid-ureter, traversing the region that overlies the sacrum. The distal

ureter, a shorter segment positioned between the inferior margin of the sacrum and the ureteral orifice.

The Surveillance, Epidemiology, and End Results program recorded 13,800 UTUC cases between 1973 and 2005 [11]. The UTUC incidence increased from 1.88–2.06 cases per 100,000 person-years during this period. Ureter cancer incidence rose from 0.69–0.91 cases per 100,000 person-years, while renal pelvis cancer slightly decreased from 1.19–1.15 cases per 100,000 person-years [11]. Ureter cancer now accounts for 33–46% of all UTUC cases [11-14].

Treatment of UTUC

RNU with bladder cuff excision remains the standard treatment for UTUC. Advanced T and N stages, tumor grade, size, multiple tumors, and positive lympho-vascular invasion (LVI) are independent prognostic factors affecting survival rates post-RNU [15].

Postoperative recurrences are common, occurring in the bladder (22–47%), locoregionally (20%), distant metastasis (10–20%), and the contralateral upper tract (0.8–6%) [8, 16-19]. Intravesical recurrence is the most prevalent, affecting up to 30% of patients within 24 months postoperatively [17]. Intravesical recurrence correlates with poor cancer-specific survival (CSS) [20]. The multiple recurrent bladder cancer is a risk factor for the development of UTUC [21].

In patients without a history of bladder cancer, early intravesical recurrence within 6 months is a significant predictor for undergoing radical cystectomy [22]. The recurrence of contralateral upper tract post-RNU is relatively uncommon, with an estimated incidence ranging from 0.8–6%. However, the associated risk of subsequent renal function deterioration can be severe, potentially necessitating dialysis [23, 24].

RNU may lead to decreased renal function due to ipsilateral kidney loss, posing challenges for adjuvant chemotherapy. The POUT randomized controlled trial showed the benefit of initiating cisplatin-based chemotherapy after RNU, particularly in patients with locally advanced UTUC (≥ pT2 or ≥ N1) [25]. This emphasizes the growing clinical significance of kidney sparing surgery (KSS).

KSS vs. RNU

Typical surgical indications for KSS include having a single kidney, experiencing renal insufficiency, bilateral UTUC, and other comorbidities that impede RNU. European Association of Urology (EAU) guidelines classify UTUC patients into low- and high-risk categories [14]. Low-risk patients exhibit unifocal disease, tumor size <2 cm, low-grade cytology and/or URS biopsy results, and noninvasive findings on imaging. High-risk patients show features such as hydronephrosis, multifocal disease, tumor size ≥2 cm, high-grade cytology and/or URS biopsy results, invasive imaging findings, and a history of radical cystectomy.

National Comprehensive Cancer Network (NCCN) guidelines categorize UTUC cases into those with favorable or less favorable clinical and pathological characteristics for renal preservation [26]. Favorable cases include low-grade tumors determined through cytology and biopsy, papillary, size <1.5 cm, or unifocal tumors, with cross-sectional imaging indicating no signs of invasive disease. Less favorable cases encompass tumors that are multifocal, flat, or sessile, ≥1.5 cm, high-grade, cT2-T4, mid-ureteral, or proximal ureteral due to technical complexities, and tumors extending into the infundibulum or the ureteropelvic junction.

KSS methods can be categorized into those addressing renal pelvis cancer and ureter cancer. For renal pelvis cancer, ureteroscopic tumor ablation (UTA) is commonly

employed [27]. Meanwhile, for ureter cancer, various surgical approaches are available, including UTA, distal ureterectomy with reimplantation (DU), ileal ureter replacement (IU), and ureterectomy with ureteroureterostomy (UU) [28]. UTA techniques typically involve an initial reduction in tumor size using a cold cup or basket, followed by treatment using electrocautery or laser ablation [29]. DU for high-risk UTUC may yield comparable oncological outcomes to RNU [30]. IU surgery, entailing complete ureter removal and the creation of an ileal-ureteral substitution, may be considered for low-risk cases and, in highly selective patients, for mid to proximal ureter tumors [31].

KSS offers a reduction in morbidity compared to RNU concerning renal function [32]. KSS may help prevent potential long-term cardiovascular complications by lowering the risk of renal function impairment associated with nephron loss during RNU [33]. Unlike renal pelvis cancer, ureter cancer presents a wider array of anatomically diverse kidney-sparing surgical options. This distinction is attributed to the ability to resect different locations of ureter cancer through IU surgery, an option not available for renal pelvis cancer [34]. However, existing guidelines primarily emphasize disease risk-based management and do not differentiate between renal pelvis cancer and ureter cancer [14, 35].

Research purpose

The primary objective of this study is to identify the conditions for employing KSS approaches in patients with ureter cancer. A retrospective analysis of the entire UTUC cohort that underwent surgical treatment at Asan Medical Center from 2011-2019 revealed tumor unifocality as a significant prognostic factor. Recognizing the importance of tumor unifocality in the context of ureter cancer, I delve into the reasons for selecting KSS, with a specific focus on unifocal ureter cancer (UUC). I also examine various

prognostic factors, including renal function, tumor size, grade, location, and clinical pathologic stage, to determine the appropriate surgical approach for UUC. Building upon these insights, I propose a tailored management approach specific to ureter cancer, complementing existing guidelines.

MATERIALS AND METHODS

Retrospective review of total 708 consecutive UTUC in Asan Medical Center

A retrospective review was conducted at Asan Medical Center involving 708 patients with UTUC who underwent either RNU (N = 646) or KSS (N = 62) between 2011 and 2019. The institutional ethics board approved this study, and informed consent was waived (IRB No: 2022-1133). Data were collected from electronic patient records and securely stored in an encrypted database. The data were gathered from the patient's initial presentation until their last follow-up, and imaging data from computed tomography (CT) and magnetic resonance imaging (MRI) were thoroughly reviewed.

Cystoscopy was initially conducted every 3 months for the first 1-2 years, followed by every 6 months for the next 1-2 years, and then annually thereafter. Imaging follow-up was initially performed at 3 months, then every 6 months for 2-3 years, and subsequently annually. The determination of tumor unifocality was primarily based on ureteroscopy and CT urography. In cases where the tumor was too long for the ureteroscope to pass the upper margin of the tumor, tumor unifocality was determined using CT urography.

Analysis of clinicopathologic and prognostic factors in total cohort

The analysis encompassed the entire UTUC cohort (N = 708), examining prognostic factors, survival rates for different treatments (RNU vs. KSS), and whether post-surgery estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2. The characteristics of the entire UTUC cohort (N=708) are shown in Table 1. Among the 708 patients diagnosed with UTUC and treated, 646 (91.2%) underwent RNU, while 62 (8.8%) underwent KSS. The participants had an average age of 68.2 years, and the mean follow-up duration was

68.0 months. Patient characteristics were well-balanced in terms of preoperative eGFR and tumor location. However, the RNU group showed a higher prevalence of larger tumor size, high-grade tumors, and advanced stage (≥ pT2), while the KSS group had more unifocal tumors.

Table 1. Clinicopathological characteristics of patients with UTUC

Characteristics	Overall	RNU	KSS	P
N (%)	708 (100.0)	646 (91.2)	62 (8.8)	
Age, year, mean ± SD	68.2 ± 10.1	68.3 ± 10.1	67.7 ± 9.9	0.691
Sex, n (%)				0.175
Male	507 (71.6)	458 (70.9)	49 (79.0)	
Female	201 (28.4)	188 (29.1)	13 (21.0)	
BMI, kg/m^2, mean ± SD	24.6 ± 3.1	24.6 ± 3.1	24.8 ± 3.3	0.598
Preoperative eGFR, mL/min/1.73 m^2, mean ± SD	67.9 ± 21.2	68.5 ± 20.6	61.7 ± 26.6	0.098
Tumor size [a], cm, mean ± SD	3.6 ± 2.8	3.7 ± 2.8	2.3 ± 1.6	0.000
Tumor grade, n (%)				0.000
High grade	564 (79.7)	526 (81.4)	38 (61.3)	
Low grade	122 (17.2)	105 (16.3)	17 (27.4)	
Non	22 (3.1)	15 (2.3)	7 (11.3)	
CIS, n (%)	290 (41.0)	267 (41.3)	23 (37.1)	0.581
Lymphovascular invasion, n (%)	168 (23.7%)	164 (25.4)	4 (6.5%)	0.731
Pathologic stage, n (%)				0.000
T0	11 (1.6)	6 (0.9)	5 (8.1)	
Tis	19 (2.7)	16 (2.5)	3 (4.8)	
Ta	165 (23.3)	145 (22.4)	20 (32.3)	
T1	174 (24.6)	161 (24.9)	13 (21.0)	
T2	86 (2.1)	77 (11.9)	9 (14.5)	
T3	228 (32.2)	216 (33.4)	12 (4.8)	
T4	25 (3.5)	25 (3.9)	0 (0.0)	
Node positive, n (%)	55 (7.8)	54 (8.4)	1 (1.6)	0.058
Variant histology, n (%)	146 (20.6)	138 (21.4)	8 (12.9)	0.455
Tumor location, n (%)				0.536
Renal pelvis alone	227 (32.1)	220 (34.1)	7 (11.3)	
Ureter alone	347 (49.0)	292 (45.2)	55 (88.7)	
Renal pelvis and ureter	134 (18.9)	134 (20.7)	0 (0.0)	
Tumor multifocality, n (%)				0.000
Unifocal disease	501 (70.8)	444 (68.7)	57 (91.9)	
Multifocal disease	207 (29.2)	202 (31.3)	5 (8.1)	

Abbreviations: BMI=body mass index; CIS=carcinoma in situ; eGFR=estimated glomerular filtration rate; KSS=kidney sparing surgery; N=number of patients; Non=tumors with unanalyzed grades; RNU=radical nephroureterectomy

[a] Tumor size is based on the length of main tumor

Subgroup analysis of prognostic factor in ≤pT1

Generally, the tumor, node, metastasis (TNM) classification serves as a potent tool for evaluating the prognosis and disease status of UTUC patients [36]. Advanced stage (≥ pT2) and node positivity were identified as significant risk factors through Cox multivariate analysis of the entire UTUC cohort. Subgroup analyses focused on non-invasive (≤pT1) tumors and ≤pT1 ureter cancer, highlighting significant risk factors, including tumor multifocality.

Functional and oncologic outcome in patients with UUC between RNU and KSS

Among the entire cohort of 708 patients, 269 (38.0%) were diagnosed with UUC. In this subset, a comparison of 4 weeks post-surgery eGFR changes was made between RNU (N = 219, 81.4%) and KSS (N = 50, 18.6%). In UUC subgroup, Intravesical recurrence-free survival (IRFS), metastasis-free survival (MFS), CSS, and overall survival (OS) were compared between the RNU (N=219) and KSS (N=50). For the MFS parameter, this study excluded bladder and ipsilateral ureter tumor recurrences and included metastases to various organs, such as lymph nodes, lung, liver, bone, and more. In cases where the cause of death was uncertain, a consensus meeting was conducted to accurately determine the cause of death.

Table 2 presents the characteristics of the UUC cohort (N=269). In general, there was a relatively even distribution of preoperative eGFR, tumor size, node involvement, variant histology, and high-grade tumor between the two surgical groups. However, a disparity in the distribution of pathologic stages between the RNU and KSS groups was observed, primarily due to a higher prevalence of advanced stage (≥pT2) in the RNU group. To address this imbalance, this study implemented propensity score matching to ensure an equitable distribution of prognostic factors between the two surgical groups, as shown in

Table 3.

This study conducted a subgroup analysis of high-grade UUC patients (N=207) to assess survival outcomes and prognostic factors in patients undergoing RNU and KSS. Table 4 presents the characteristics of the high-grade UUC cohort. An uneven distribution of preoperative eGFR between the RNU and KSS groups was observed, primarily due to the inclusion of 9 cases with a single kidney in the KSS group (Mean eGFR: RNU vs. KSS; 65.8 vs. 53.1 mL/min/1.73 m^2; P = 0.010). To address this disparity, the study employed propensity score matching to ensure a balanced distribution of prognostic factors between the two surgical groups (as shown in Table 5).

Table 2. Clinicopathological characteristics of patients with unifocal ureter cancer

Characteristics	Overall	RNU	KSS	P
N (%)	269 (100.0)	219 (81.4)	50 (18.6)	
Age, year, mean ± SD	68.7 ± 9.2	68.8 ± 9.1	68.3 ± 9.9	0.735
Sex, n (%)				0.474
Male	199 (74.0)	160 (73.1)	39 (78.0)	
Female	70 (26.0)	59 (26.9)	11 (22.0)	
BMI, kg/m^2, mean ± SD	24.8 ± 3.1	24.8 ± 3.1	24.9 ± 3.2	0.663
Preoperative eGFR, mL/min/1.73 m^2, mean ± SD	65.3 ± 21.5	66.8 ± 20.1	58.8 ± 26.1	0.095
Tumor size, cm, mean ± SD	2.7 ± 1.5	2.7 ± 1.5	2.4 ± 1.7	0.252
Tumor grade, n (%)				0.096
High grade	207 (77.0)	173 (79.0)	34 (68.0)	
Low grade	50 (18.6)	40 (18.3)	10 (20.0)	
Non	12 (4.4)	6 (2.7)	6 (12.0)	
CIS, n (%)	106 (39.4)	88 (40.2)	18 (36.0)	0.587
Pathologic stage, n (%)				0.001
T0	10 (3.7)	5 (2.3)	5 (10.0)	
Tis	8 (3.0)	6 (2.7)	2 (4.0)	
Ta	53 (19.7)	40 (18.3)	13 (26.0)	
T1	59 (21.9)	47 (21.5)	12 (24.0)	
T2	44 (16.4)	37 (16.9)	7 (14.0)	
T3	92 (34.2)	81 (37.0)	11 (22.0)	
T4	3 (1.1)	3 (1.4)	0 (0.0)	
Node positive, n (%)	17 (6.3)	16 (7.3)	1 (2.0)	0.165
Variant histology, n (%)	50 (18.6)	43 (16.0)	7 (14.0)	0.357

Abbreviations: BMI=body mass index; CIS=carcinoma in situ; eGFR=estimated glomerular filtration rate; KSS=kidney sparing surgery; N=number of patients; RNU=radical nephroureterectomy

Table 3. Clinicopathological characteristics of patients with unifocal ureteral cancer after propensity score matching

Characteristics	Overall	RNU	KSS	P
N (%)	100 (100.0)	50 (50.0)	50 (50.0)	
Unifocality, n (%)	100 (100.0)	50 (100.0)	50 (100.0)	
Age, year, mean ± SD	67.5 ± 9.2	66.7 ± 8.5	68.3 ± 9.9	0.387
Sex, n (%)				0.621
Male	80 (80.0)	41 (82.0)	39 (78.0)	
Female	20 (20.0)	9 (18.0)	11 (22.0)	
BMI, kg/m^2, mean ± SD	24.7 ± 3.0	24.5 ± 2.8	24.9 ± 3.2	0.517
Preoperative eGFR, mL/min/1.73 m^2, mean ± SD	58.9 ± 23.0	59.0 ± 19.6	58.8 ± 26.1	0.956
Tumor size, cm, mean ± SD	2.5 ± 1.4	2.5 ± 1.1	2.4 ± 1.7	0.593
High grade, n (%)	69 (69.0)	35 (70.0)	34 (68.0)	0.831
CIS, n (%)	33 (33.0)	15 (30.0)	18 (36.0)	0.528
Advanced pathologic stage (≥pT2), n (%)	37 (37.0)	19 (38.0)	18 (36.0)	0.838

Abbreviations: BMI=body mass index; CIS=carcinoma in situ; eGFR=estimated glomerular filtration rate; KSS=kidney sparing surgery; N=number of patients; RNU=radical nephroureterectomy

Table 4. Clinicopathological characteristics of patients with high-grade and unifocal ureter cancer

Characteristics	Overall	RNU	KSS	P
N (%)	207 (100.0)	173 (83.6)	34 (16.4)	
Age, year, mean ± SD	68.9 ± 9.6	69.0 ± 9.4	68.5 ± 10.5	0.757
Sex, n (%)				0.466
Male	154 (74.4)	127 (73.4)	27 (79.4)	
Female	53 (25.6)	46 (26.6)	7 (20.6)	
BMI, kg/m^2, mean ± SD	24.9 ± 3.2	24.9 ± 3.1	24.9 ± 3.3	0.916
Preoperative eGFR, mL/min/1.73m^2, mean ± SD	63.7 ± 21.6	65.8 ± 20.0	53.1 ± 26.3	0.010
Tumor size, cm, mean ± SD	2.7 ± 1.5	2.7 ± 1.5	2.6 ± 1.8	0.721
CIS, n (%)	96 (46.4)	81 (46.8)	15 (44.1)	0.774
Pathologic stage, ≥pT2, n (%)	137 (66.2)	119 (86.9)	18 (52.9)	0.075
Distal ureter	130 (62.8)	109 (63.0)	21 (61.8)	0.892
Variant histology, n (%)	47 (22.7))	41 (23.7))	6 (17.6)	0.444

Abbreviations: BMI=body mass index; CIS=carcinoma in situ; eGFR=estimated glomerular filtration rate; KSS=kidney sparing surgery; N=number of patients; RNU=radical nephroureterectomy; UTUC=upper tract urothelial carcinoma

Table 5. Clinicopathological characteristics of patients with high-grade and unifocal ureter cancer after propensity score matching

Characteristics	Overall	RNU	KSS	P
N (%)	68 (100.0)	34 (50.0)	34 (50.0)	
Unifocality, n (%)	68 (100.0)	34 (100.0)	34 (100.0)	
High-grade, n (%)	68 (100.0)	34 (100.0)	34 (100.0)	
Age, year, mean ± SD	67.6 ± 10.4	66.8 ± 10.3	68.5 ± 10.5	0.509
Sex, n (%)				0.762
Male	55 (80.9)	28 (82.4)	27 (79.4)	
Female	13 (19.1)	6 (17.6)	7 (20.6)	
BMI, kg/m^2, mean ± SD	24.7 ± 3.1	24.5 ± 2.9	24.9 ± 3.3	0.664
Preoperative eGFR, mL/min/1.73 m^2, mean ± SD	55.5 ± 22.2	57.8 ± 17.3	53.1 ± 26.3	0.364
Tumor size, cm, mean ± SD	2.8 ± 1.7	2.9 ± 1.7	2.6 ± 1.8	0.489
CIS, n (%)	29 (42.6)	14 (41.2)	15 (44.1)	0.810
Distal ureter, n (%)	47 (69.1)	26 (76.5)	21 (61.8)	0.193
Advanced pathologic stage (≥pT2), n (%)	32 (47.1)	14 (41.2)	18 (52.9)	0.338
Variant histology, n (%)	13 (19.1)	7 (20.6)	6 (17.6)	0.762

Abbreviations: BMI=body mass index; CIS=carcinoma in situ; eGFR=estimated glomerular filtration rate; KSS=kidney sparing surgery; N=number of patients; RNU=radical nephroureterectomy

A subgroup analysis of patients with large (≥2 cm) UUC was conducted to evaluate survival outcomes between RNU and KSS. The characteristics of the large (≥2 cm) UUC cohort (N=175) are shown in Table 6. An imbalance was observed in the distribution of preoperative eGFR between the RNU and KSS groups, primarily due to the inclusion of 6 cases with single kidney in the KSS group (mean eGFR: RNU vs. KSS; 64.9 vs. 51.7, mL/min/1.73 m^2; P=0.014). To rectify this disparity, propensity score matching was employed to ensure an equitable distribution of prognostic factors between the two surgical groups (as shown in Table 7).

To compare variables, I used either Student's t-test or the Mann-Whitney U test. For analyzing IRFS, MFS, CSS, and OS, I utilized Kaplan-Meier survival curves and the log-rank test. Cox proportional hazard regression model was also used to identify prognostic factors. The statistical significance level was set at a p-value of less than 0.05, and all statistical analyses were performed using SPSS software (version 28.0; SPSS Inc., Chicago, IL, USA).

Table 6. Clinicopathological characteristics of patients with large (≥2cm) and unifocal ureter cancer

Characteristics	Overall	RNU	KSS	P
N (%)	175 (100.0)	149 (85.1)	26 (14.9)	
Age, year, mean ± SD	69.3 ± 9.5	69.0 ± 9.5	71.1 ± 9.7	0.301
Sex, n (%)				0.937
Male	129 (73.7)	110 (73.8)	19 (73.1)	
Female	46 (26.3)	39 (26.2)	7 (26.9)	
BMI, kg/m^2, mean ± SD	24.6 ± 3.0	24.6 ± 2.9	24.4 ± 3.9	0.732
Preoperative eGFR, mL/min/1.73 m^2, mean ± SD	62.9 ± 22.5	64.9 ± 21.0	51.7 ± 27.6	0.014
Tumor size, cm, mean ± SD	3.4 ± 1.4	3.4 ± 1.4	3.4 ± 1.7	0.832
Tumor grade, n (%)				0.437
High grade	138 (78.9)	119 (79.9)	19 (73.1)	
Low grade	33 (18.9)	27 (18.1)	6 (23.1)	
Non	4 (2.2)	3 (2.0)	1 (3.8)	
CIS, n (%)	61 (34.9)	53 (35.6)	8 (30.8)	0.638
Pathologic stage, n (%)				0.052
T0	5 (2.9)	3 (2.0)	2 (7.7)	
Tis	2 (1.1)	2 (1.3)	0 (0.0)	
Ta	36 (20.6)	28 (18.8)	8 (30.8)	
T1	42 (24.0)	36 (24.2)	6 (23.1)	
T2	31 (17.7)	27 (18.1)	4 (15.4)	
T3	57 (32.6)	51 (34.2)	6 (23.1)	
T4	2 (1.1)	2 (1.3)	0 (0.0)	
Variant histology, n (%)	35 (20.0%)	30 (20.1)	5 (19.2)	0.916

Abbreviations: BMI=body mass index; CIS=carcinoma in situ; eGFR=estimated glomerular filtration rate; KSS=kidney sparing surgery; N=number of patients; RNU=radical nephroureterectomy; UTUC=upper tract urothelial carcinoma

Table 7. Clinicopathological characteristics of patients with large (≥2cm) and unifocal ureter cancer after propensity score matching

Characteristics	Overall	RNU	KSS	P
N (%)	52 (100.0)	26 (50.0)	26 (50.0)	
Unifocality, n (%)	52 (100.0)	26 (100.0)	26 (100.0)	
Tumor size (≥2cm), n (%)	52 (100.0)	26 (100.0)	26 (100.0)	
Age, year, mean ± SD	69.5 ± 9.8	67.8 ± 9.8	71.1 ± 9.7	0.240
Sex, n (%)				0.248
Male	34 (65.4)	15 (57.7)	19 (73.1)	
Female	18 (34.0)	11 (42.3)	7 (26.9)	
BMI, kg/m^2, mean ± SD	24.3 ± 3.2	24.1 ± 2.3	24.4 ± 3.9	0.725
Preoperative eGFR, mL/min/1.73 m^2, mean ± SD	58.1 ± 23.1	64.6 ± 15.5	51.7 ± 27.6	0.064
Tumor size, cm, mean ± SD	3.5 ± 1.6	3.5 ± 1.4	3.4 ± 1.7	0.944
High grade, n (%)	39 (75.0)	20 (76.9)	19 (73.1)	0.755
CIS, n (%)	18 (34.6)	10 (38.5)	8 (30.8)	0.569
Advanced pathologic stage (≥pT2), n (%)	26 (50.0)	16 (61.5)	10 (38.5)	0.100

Abbreviations: BMI=body mass index; CIS=carcinoma in situ; eGFR=estimated glomerular filtration rate; KSS=kidney sparing surgery; N=number of patients; RNU=radical nephroureterectomy

Analysis of renal function loss and clinical consequences following RNU and KSS

In the total UTUC cohort (N = 708), an analysis of eGFR showed a decrease at 4 weeks after RNU was conducted, compared with a slight increase for KSS. Specific attention was given to the number of RNU patients with post-surgery eGFR <50 mL/min/1.73 m^2 in advanced stage (≥pT2).

Using technetium-99m diethylene triamine penta-acetic acid [99mTc-DTPA] renography, contralateral renal function (CRF) (≥50 mL/min/1.73 m^2 or <50 mL/min/1.73 m^2) and ipsilateral renal function (IRF) (≥30 mL/min/1.73 m^2 or <30 mL/min/1.73 m^2) were assessed preoperatively. Additionally, subclassification was performed to conduct the same analysis in both the pure ureter cancer (PUC) group and the UUC group.

Approaches for KSS in UUC

The clinicopathological characteristics of four KSS approaches (DU, IU, UTA, and UU) were presented (Table 8). In the cohort of UUC (N=269), the choice of each kidney-sparing surgical method was made considering various factors, including renal function, tumor grade, size, location, and more. A retrospective analysis evaluated CSS for each approach in the UUC cohort.

Table 8. Clinicopathological Characteristics of Patients who underwent KSS in unifocal ureter cancer

Characteristics	DU	IU	UTA	UU
N (%)	29 (58.0)	13 (26.0)	3 (6.0)	5 (10.0)
Age, year, mean ± SD	68.3 ± 9.9	65.6 ± 10.5	66.0 ± 6.6	77.2 ± 4.8
Sex, n (%)				
Male	22 (75.9)	10 (76.9)	3 (100.0)	4 (80.0)
Female	7 (24.1)	3 (23.1)	0 (0.0)	1 (20.0)
BMI, kg/m^2, mean ± SD	25.5 ± 2.9	24.9 ± 3.6	25.8 ± 1.0	21.2 ± 2.1
Preoperative eGFR, mL/min/1.73 m^2, mean ± SD	65.3 ± 25.9	57.9 ± 24.0	50.3 ± 25.6	28.8 ± 10.9
Tumor size, cm, mean ± SD	2.2 ± 1.6	2.3 ± 2.1	1.2 ± 0.76	2.4 ± 0.6
Tumor grade, n (%)				
High grade	20 (69.0)	7 (53.8)	2 (66.7)	5 (100.0)
Low grade	5 (17.2)	4 (30.8)	1 (33.3)	0 (0.0)
Non	4 (13.8)	2 (15.4)	0 (0.0)	0 (0.0)
CIS, n (%)	13 (44.8)	2 (15.4)	0 (0.0)	3 (60.0)
Pathologic stage, n (%)				
T0	2 (6.9)	3 (23.1)	0 (0.0)	0 (0.0)
Tis	2 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)
Ta	5 (17.2)	4 (30.8)	3 (100.0)	1 (20.0)
T1	9 (31.0)	2 (15.4)	0 (0.0)	1 (20.0)
T2	6 (20.7)	0 (0.0)	0 (0.0)	2 (40.0)
T3	5 (17.2)	4 (30.8)	0 (0.0)	1 (20.0)
T4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tumor location, n (%)				
Proximal	0	4 (30.8)	0 (0.0)	3 (60.0)
Mid	0	8 (61.5)	2 (66.7)	2 (40.0)
Distal	29 (100.0)	1 (7.7)	1 (33.3)	0 (0.0)
Node positive, n (%)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)
Variant histology, n (%)	3 (10.3)	2 (15.4)	0 (0.0)	2 (40.0)

Abbreviations: BMI=body mass index; CIS=carcinoma in situ; DU=distal ureterectomy with reimplantation; eGFR=estimated glomerular filtration rate; IU=ileal ureter replacement; N=number of patients; RNU=radical nephroureterectomy; KSS=kidney sparing surgery; UTA=ureteroscopic tumor ablation; UU= ureterectomy with ureteroureterostomy

Selection of possible candidate for KSS in patients who underwent RNU in PUC

Among patients with PUC who underwent RNU (N=292) (as shown in Table 9), this study excluded typical surgical indications for KSS, such as having a single kidney (N=2), CKD stage 4 or below (N=15). Additionally, patients with CRF ≥50 mL/min/1.73 m^2 and IRF <30 mL/min/1.73 m^2 (N=72) were excluded, indicating that they should undergo RNU as the primary treatment. After this rigorous selection process, 205 candidates were identified eligible for KSS, among whom 152 had UUC. Among these 152 patients, KSS was recommended based on factors such as tumor stage, grade, size, location, patient's motivation for renal preservation, and split renal function. Drawing upon these analyses, I aim to propose a tailored management approach specific to ureter cancer.

Table 9. Clinicopathological characteristics of patients with pure ureter cancer

Characteristics	Overall	RNU	KSS	P
N (%)	347 (100.0)	292 (84.1)	55 (15.9)	
Age, year, mean ± SD	69.1 ± 9.2	69.3 ± 9.0	68.2 ± 10.2	0.427
Sex, n (%)				0.195
Male	246 (70.9)	203 (69.5)	43 (78.2)	
Female	101 (29.1)	89 (30.5)	12 (21.8)	
BMI, kg/m^2, mean ± SD	24.7 ± 3.1	24.6 ± 3.1	24.9 ± 3.3	0.480
Preoperative eGFR, mL/min/1.73 m^2, mean ± SD	64.9 ± 21.5	65.9 ± 20.4	59.1 ± 25.9	0.111
Tumor size, cm, mean ± SD	2.8 ± 2.0	2.9 ± 2.1	2.4 ± 1.6	0.063
Tumor grade, n (%)				0.445
High grade	273 (78.7)	235 (80.5)	38 (69.1)	
Low grade	55 (15.9)	45 (15.4)	10 (18.2)	
Non	19 (5.5)	12(4.1)	7 (12.7)	
CIS, n (%)	173 (49.9)	150 (51.4)	23 (41.8)	0.194
Pathologic stage, n (%)				0.001
T0	10 (2.9)	5 (1.7)	5 (9.1)	
Tis	15 (4.3)	12 (4.1)	3 (5.5)	
Ta	58 (16.7)	45 (15.4)	13 (23.6)	
T1	76 (21.9)	63 (21.6)	13 (23.6)	
T2	67 (19.3)	58 (19.9)	9 (16.4)	
T3	117 (33.7)	105 (36.0)	12 (21.8)	
T4	4 (1.2)	4 (1.4)	0 (0.0)	
Node positive, n (%)	22 (6.3)	21 (7.2)	1 (1.8)	0.134
Variant histology, n (%)	63 (18.2)	55 (18.8)	8 (14.5)	0.450
Multifocality, n (%)	78 (22.5)	73 (25.0)	5 (9.1)	0.010

Abbreviations: BMI=body mass index; CIS=carcinoma in situ; eGFR=estimated glomerular filtration rate; KSS=kidney sparing surgery; N=number of patients; RNU=radical nephroureterectomy

RESULTS

Clinicopathologic and prognostic factors in total 708 consecutive UTUC in Asan Medical Center

Among the 708 patients diagnosed with UTUC, 646 (91.2%) underwent RNU, while 62 (8.8%) underwent KSS. Analysis of the entire cohort revealed that there were no significant differences in IRFS, MFS, CSS, or OS between the RNU and KSS groups (Figure 1).

Intravesical tumor recurrence was observed in 40.9 and 35.5% of RNU and KSS cases, respectively (P = 0.398). Metastases were identified in various locations, including lymph nodes (N = 86), lung (N = 42), liver (N = 21), bone (N = 13), contralateral kidney (N = 8), peritoneum (N = 6), muscle (N = 3), adrenal gland (N = 2), and rectum (N = 1). There was no significant difference in the incidence of metastases between the RNU and KSS groups (RNU vs. KSS; 25.5% vs. 27.4%; P = 0.796). CSS rates showed no significant difference, with a mortality rate of 28.6 and 24.6% for RNU and KSS, respectively (P = 0.644). OS rates were similar, with 5- and 10-year rates of 70.6 and 50.9% vs. 71.9 and 56.8% for RNU and KSS, respectively.

To analyze the risk factors for CSS in the entire UTUC cohort (N = 708), Cox multivariate analysis was conducted. Preoperative eGFR (hazard risk [HR] = 0.990, 95% confidence intervals [CI]: 0.983-0.998, P = 0.009) emerged as a significant independent predictive factor for CSS. In contrast, tumor grade (HR = 2.032, 95% CI: 1.052-3.925, P = 0.035), presence of CIS (HR = 1.492, 95% CI: 1.063-2.095, P = 0.021), pathologic stage (HR = 2.819, 95% CI: 1.949-4.076, P <0.000), and the presence of positive lymph nodes (HR = 2.151, 95% CI: 1.480-3.127, P <0.000) were identified as significant risk factors for CSS. Notably, tumor multifocality was not a significant risk factor in this

cohort (Table 10).

When performing Cox multivariate analysis in ≤pT1 UTUC (N = 369; renal pelvis cancer + ureter cancer), tumor multifocality (HR = 2.221, 95% CI: 1.231–4.010, P = 0.008) was identified as a significant independent risk factor (Table 11).

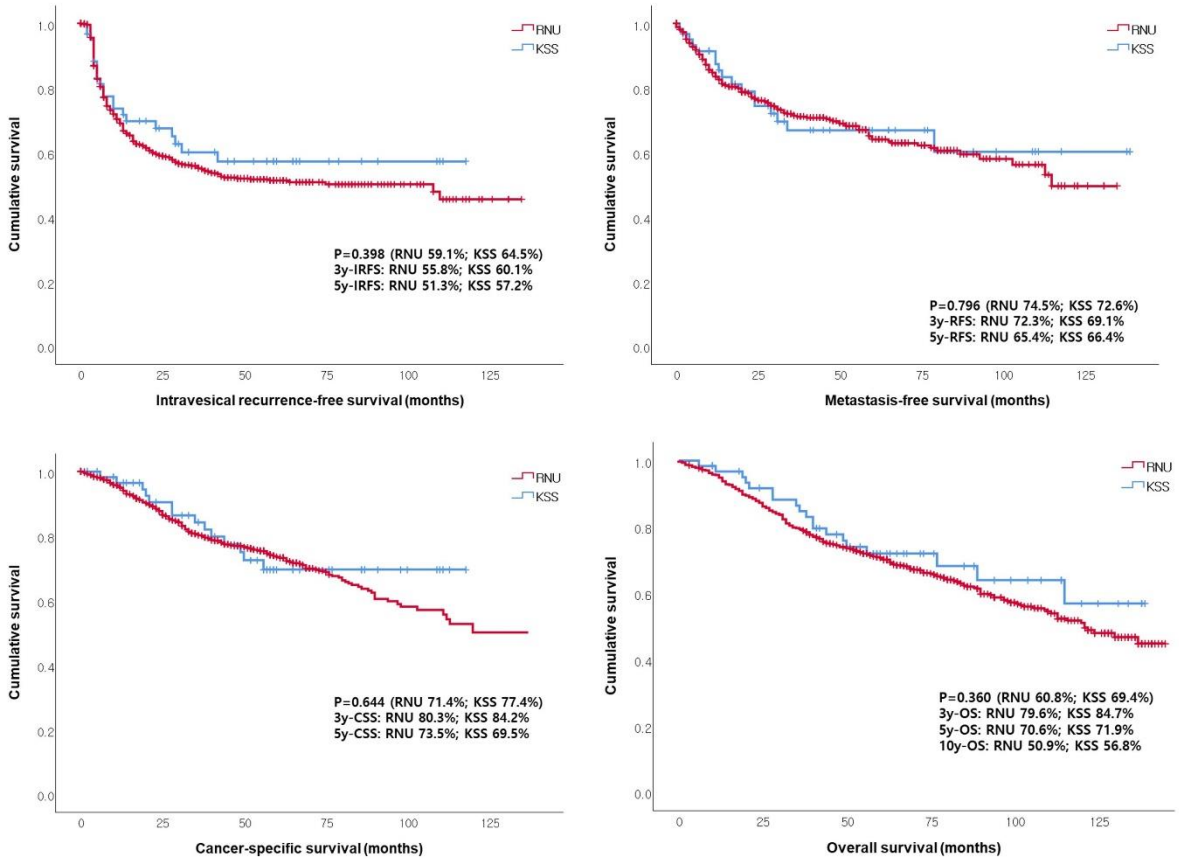


Figure 1. Survival in patients with UTUC

No significant differences in terms of IRFS, MFS, CSS, or OS between the RNU and KSS groups

Abbreviations: CSS=cancer-specific survival; IRFS=intravesical recurrence-free survival; KSS=kidney sparing surgery; MFS=metastasis-free survival; OS=overall survival; RNU=radical nephroureterectomy; UTUC=upper tract urothelial carcinoma

Table 10. Univariable and multivariable Cox regression analysis of CSS after RNU and KSS in patients with UTUC

	Univariate			Multivariate		
Variables	HR	95% CI	P	HR	95% CI	p-value
Sex	0.927	0.685-1.254	0.621			
BMI	0.928	0.883-0.975	0.003			
eGFR	0.991	0.983-0.998	0.010	0.990	0.983-0.998	0.009
Tumor size	1.009	0.963-1.057	0.702			
Tumor grade	2.056	1.064-3.973	0.032	2.032	1.052-3.925	0.035
CIS	1.525	1.073-2.166	0.018	1.492	1.063-2.095	0.021
Multifocality	1.350	0.966-1.885	0.079			
Variant histology	1.815	0.808-4.078	0.149			
Pathologic stage (≥pT2 vs ≤pT1)	2.811	1.945-4.064	<0.000	2.819	1.949-4.076	<0.000
Node positive	2.090	1.398-3.123	<0.000	2.151	1.480-3.127	<0.000

Abbreviations: BMI=body mass index; CI=confidence interval; CIS=carcinoma in situ; CSS=cancer-specific survival; eGFR=estimated glomerular filtration rate; HR=hazard ratio; KSS=kidney sparing surgery; LVI=lymphovascular invasion; RNU=radical nephroureterectomy; UTUC=upper tract urothelial carcinoma

Table 11. Univariable and multivariable Cox regression analysis of CSS after RNU and KSS in patients with non-invasive (≤pT1) UTUC

	Univariate			Multivariate		
Variables	HR	95% CI	P	HR	95% CI	P
Sex	0.920	0.476-1.779	0.804			
BMI	0.936	0.850-1.030	0.173			
eGFR	0.988	0.973-1.003	0.110			
Tumor size	1.067	0.955-1.192	0.252			
Tumor grade	2.153	1.068-4.340	0.032			
CIS	2.154	1.201-3.861	0.010			
LVI	3.608	1.289-10.100	0.015			
Variant histology	1.815	0.808-4.078	0.149			
Multifocality	2.403	1.338-4.314	0.003	2.221	1.231-4.010	0.008

Abbreviations: BMI=body mass index; CI=confidence interval; CIS=carcinoma in situ; CSS=cancer-specific survival; eGFR=estimated glomerular filtration rate; HR=hazard ratio; KSS=kidney sparing surgery; LVI=lymphovascular invasion; RNU=radical nephroureterectomy; UTUC=upper tract urothelial carcinoma

Clinical significance of unifocality for favorable clinical outcome in subgroups analysis of ≤pT1 ureter cancer

In the entire PUC cohort (N = 347), similar to the entire UTUC cohort, advanced stage (≥pT2) (HR = 2.099, 95% CI: 1.325-3.324, P = 0.002) was identified as a significant risk factor. However, tumor multifocality was not a significant risk factor (Table 12).

Based on the analysis of the entire 708 cohort of UTUC, a Cox multivariate analysis was conducted to identify risk factors for CSS in the non-invasive (≤pT1) PUC cohort (N = 159). When conducting Cox multivariate analysis for CSS in this group, tumor multifocality (HR = 2.627, 95% CI: 1.305-5.980, P = 0.019) was also identified as a significant risk factor (Table 13).

Table 12. Univariable and multivariable Cox regression analysis of CSS after RNU and KSS in patients with pure ureter cancer

	Univariate			Multivariate		
Variables	HR	95% CI	P	HR	95% CI	P
Sex	1.194	0.802–1.777	0.383			
BMI	0.933	0.874–0.996	0.038	0.929	0.870–0.991	0.026
eGFR	0.991	0.982–1.001	0.075			
Tumor size	1.028	0.926–1.141	0.605			
Tumor grade	3.019	1.222–7.458	0.017	3.012	1.227–7.395	0.016
CIS	1.398	0.895–2.184	0.140			
Multifocality	1.537	1.033–2.288	0.034			
Variant histology	1.148	0.730–1.807	0.550			
Pathologic stage (≥pT2 vs ≤pT1)	3.260	2.128–4.994	<0.000	2.099	1.325–3.324	0.002

Abbreviations: BMI=body mass index; CI=confidence interval; CIS=carcinoma in situ; CSS=cancer-specific survival; eGFR=estimated glomerular filtration rate; HR=hazard ratio; KSS=kidney sparing surgery; LVI=lymphovascular invasion; RNU=radical nephroureterectomy; UTUC=upper tract urothelial carcinoma

Table 13. Univariable and multivariable Cox regression analysis of CSS after RNU and KSS in patients with non-invasive (≤pT1) ureter cancer

	Univariate			Multivariate		
Variables	HR	95% CI	p-value	HR	95% CI	P
Sex	0.611	0.244-1.531	0.293			
BMI	0.924	0.810-1.054	0.239			
eGFR	0.990	0.970-1.010	0.308			
Tumor size	1.166	1.008-1.348	0.039			
Tumor grade	2.331	1.249-3.885	0.036			
CIS	2.080	0.940-4.603	0.071			
Variant histology	3.380	0.999-8.135	0.050			
Multifocality	2.498	1.105-5.644	0.028	2.627	1.305-5.980	0.019

Abbreviations: BMI=body mass index; CI=confidence interval; CIS=carcinoma in situ; CSS=cancer-specific survival; eGFR=estimated glomerular filtration rate; HR=hazard ratio; KSS=kidney sparing surgery; LVI=lymphovascular invasion; RNU=radical nephroureterectomy; UTUC=upper tract urothelial carcinoma

Favorable functional outcomes and compatible oncologic results of KSS in UUC compared to RNU

This study compared eGFR pre- and postoperatively at 4 weeks to evaluate changes in renal function among patients with UUC. The average change of eGFR in the RNU group (−11.2 ± 17.8 mL/min/1.73 m^2) decreased, while in the KSS group (3.1 ± 7.9 mL/min/1.73 m^2; P <0.000), it showed a slight increase.

In the UUC group (N = 269), the CSS rates showed no significant difference, with a mortality rate of 28.3% for RNU and 26.0% for KSS (P = 0.916). The OS rates were also similar, with 67.6% and 51.8% for RNU, 66.4% and 56.9% for KSS, at 5 and 10 years, respectively (P = 0.539) (Figure 2).

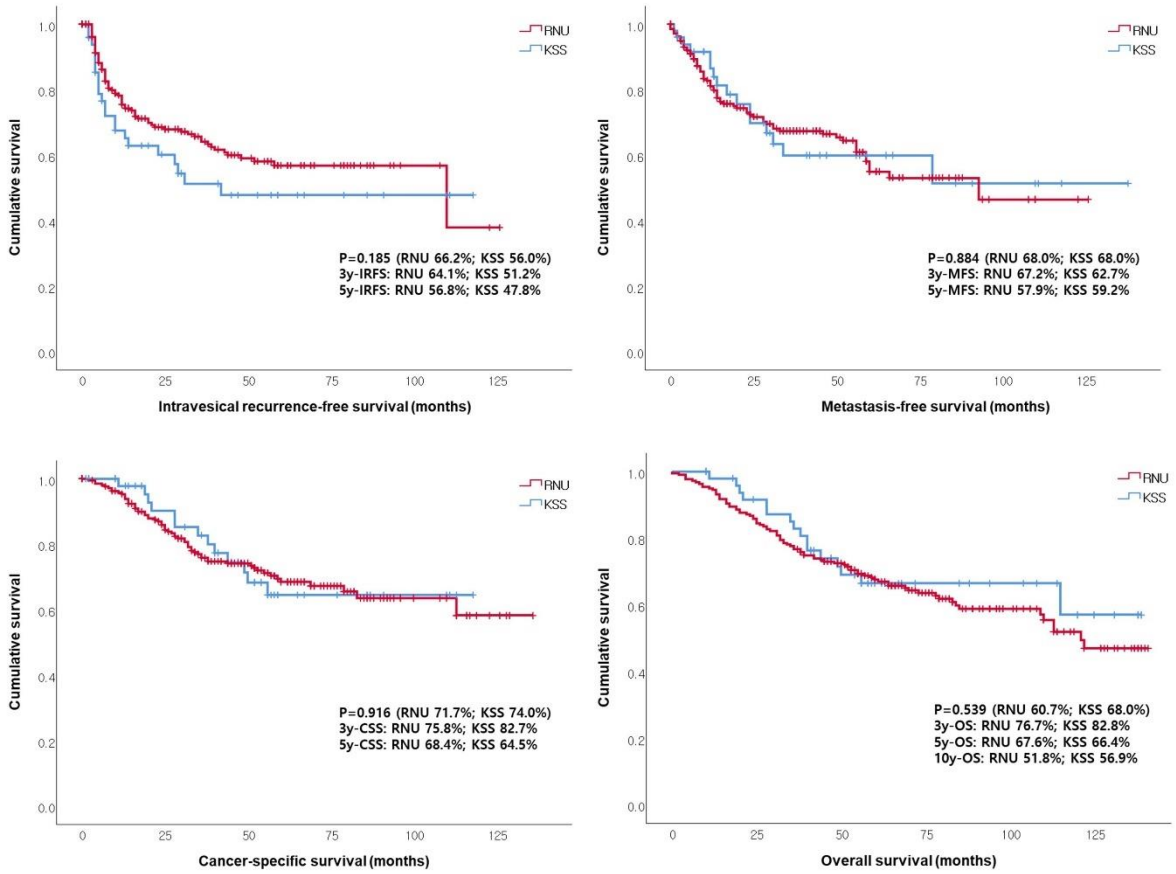


Figure 2. Survival in patients with unifocal ureter cancer

In the UUC group (N = 269), a difference in the distribution of pathological stages between the RNU and KSS groups was observed, primarily because the RNU group had a higher prevalence of advanced T stage (≥pT2). Thus, this study conducted propensity score matching to evenly distribute prognostic factors between the two surgical groups (Table 3). After 1:1 matching of the UUC group into RNU (N = 50) and KSS (N = 50) groups, Kaplan–Meier curves were utilized to analyze CSS and OS. There was no significant difference in survival rates between the two surgical methods (Figure 3). The CSS rates showed no significant difference, with mortality rates of 20.0 and 26.0% for RNU and KSS, respectively (P = 0.284). The OS rates were also similar, with 78.3 and 60.8% vs. 66.4 and 56.9% for RNU vs. KSS at 5 and 10 years, respectively (P = 0.493).

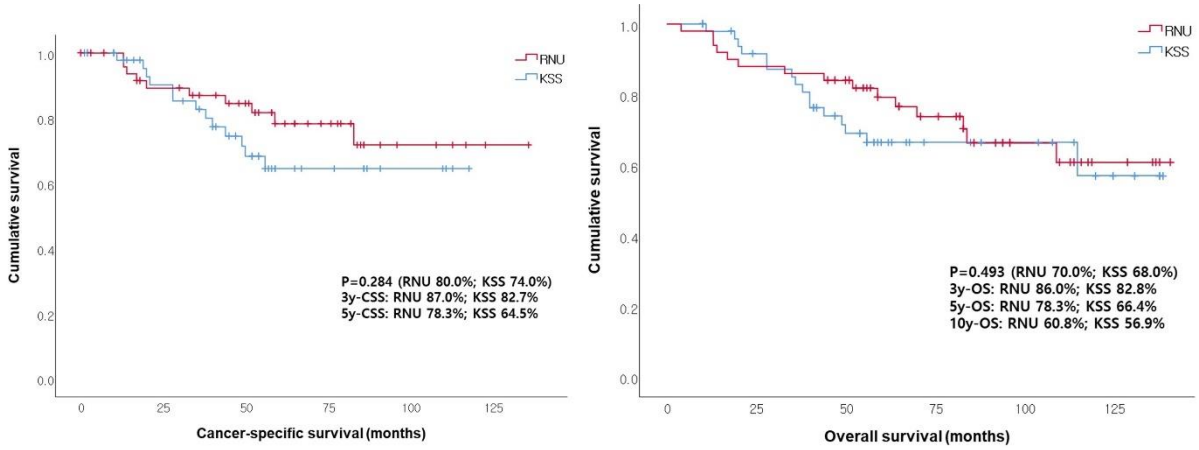


Figure 3. Survival in patients with unifocal ureter cancer after propensity score matching

In the high-grade UUC group (N = 207), there was an imbalance in the distribution of preoperative eGFR between the RNU and KSS groups (Table 4). Thus, propensity score matching was conducted to ensure a balanced distribution of prognostic factors between the two surgical groups (Table 5). Following a 1:1 matching of the high-grade patients with UUC into RNU (N = 34) and KSS (N = 34) groups, Kaplan-Meier curves were employed to analyze CSS and OS. Notably, there were no significant differences in survival rates between the two surgical methods, as shown in Figures 4 and 5. Similarly, CSS rates showed no significant difference, with a mortality rate of 38.2 and 35.3% for RNU and KSS, respectively (P = 0.492). The OS rates were also comparable, at 61.5 and 46.2% vs. 55.4 and 44.3% for RNU vs. KSS at 5 and 10 years, respectively (P = 0.615).

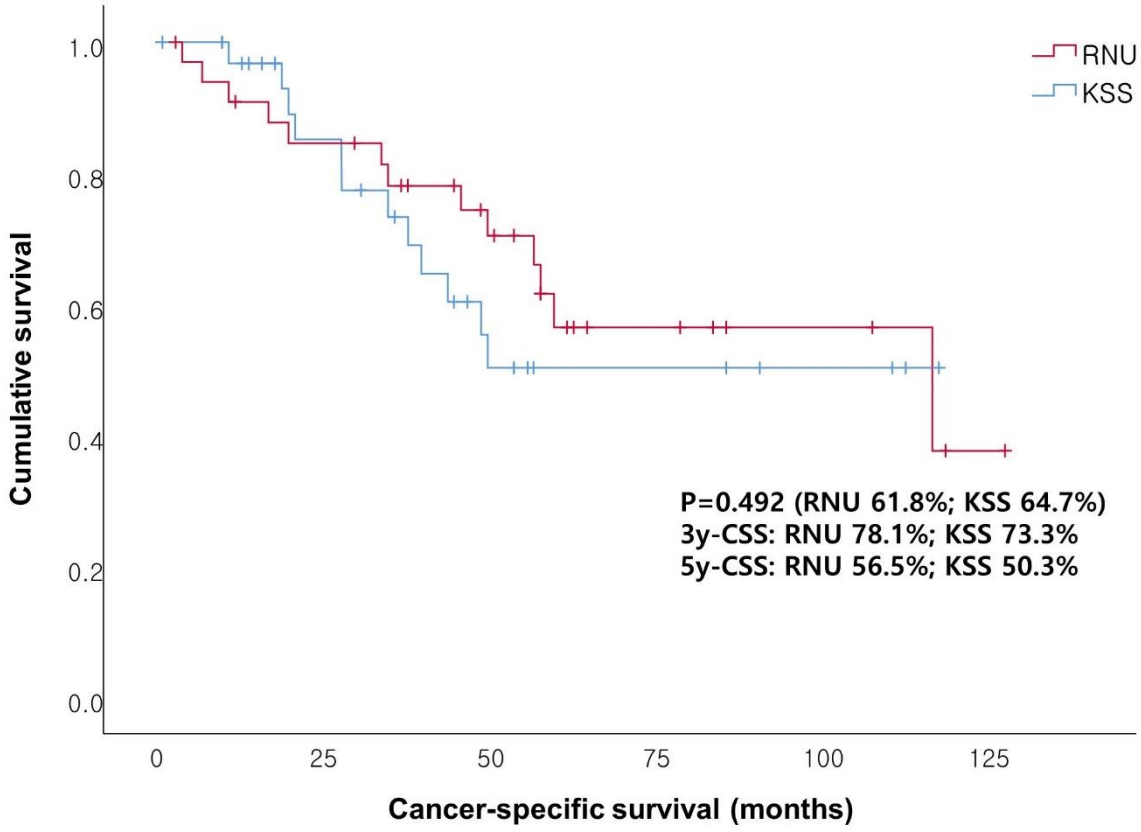


Figure 4. CSS in patients with high-grade unifocal ureter cancer after propensity score matching

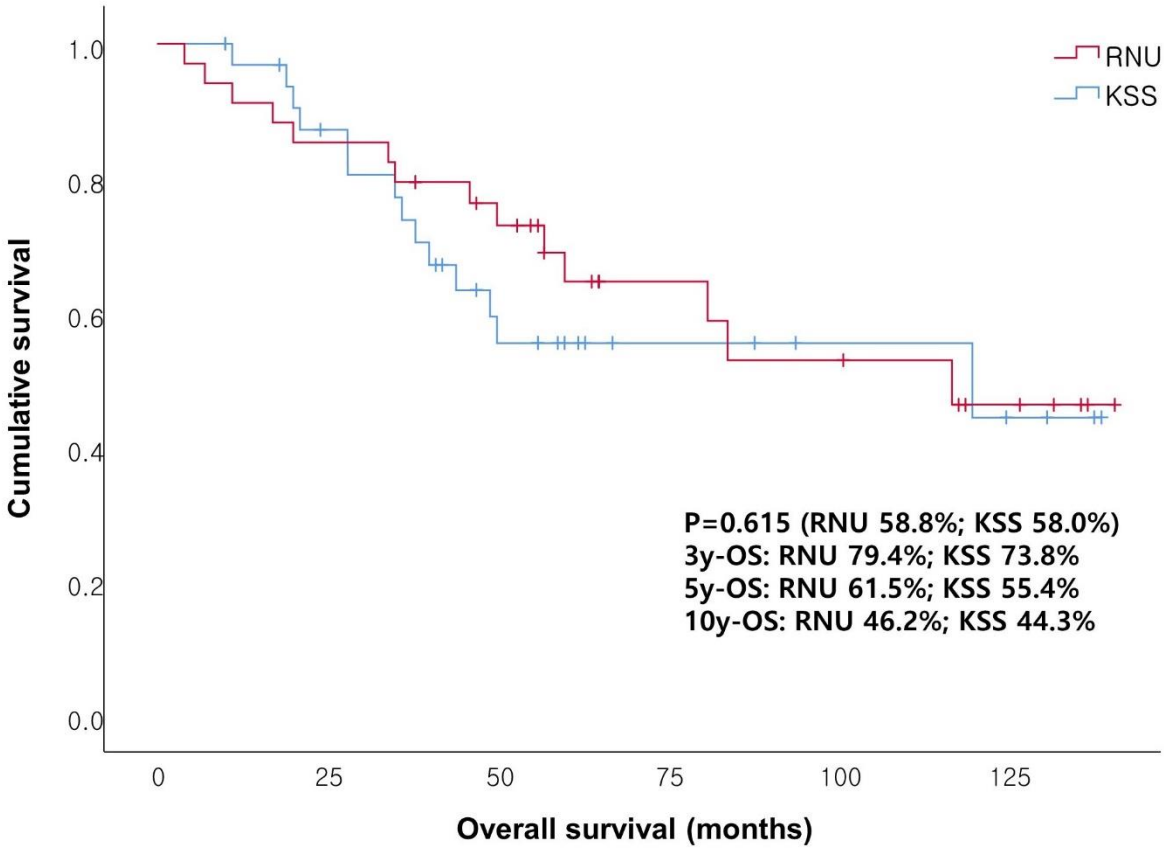


Figure 5. OS in patients with high-grade unifocal ureter cancer after propensity score matching

In the large (≥ 2 cm) UUC group (N = 175), using Kaplan–Meier analysis, there were no significant differences in IRFS, MFS, CSS, or OS between the two surgical groups (Figure 6). However, a difference in the distribution of preoperative eGFR between the RNU and KSS groups was observed (Table 6). Accordingly, propensity score matching was conducted to evenly distribute prognostic factors between the two surgical groups (Table 7). After 1:1 matching of the large UUC cohort into RNU (N = 26) and KSS (N = 26) groups, Kaplan–Meier curves were utilized to analyze CSS, and OS. There was no significant difference in survival rates between the two surgical methods (Figures 7 and 8). The CSS rates showed no significant difference, with a mortality rate of 16.4 vs. 26.9% for RNU and KSS, respectively (P = 0.262). The OS rates were also similar, at 76.9 and 46.2% vs. 69.5 and 69.5% for RNU vs. KSS at 5 and 10 years, respectively (P = 0.890).

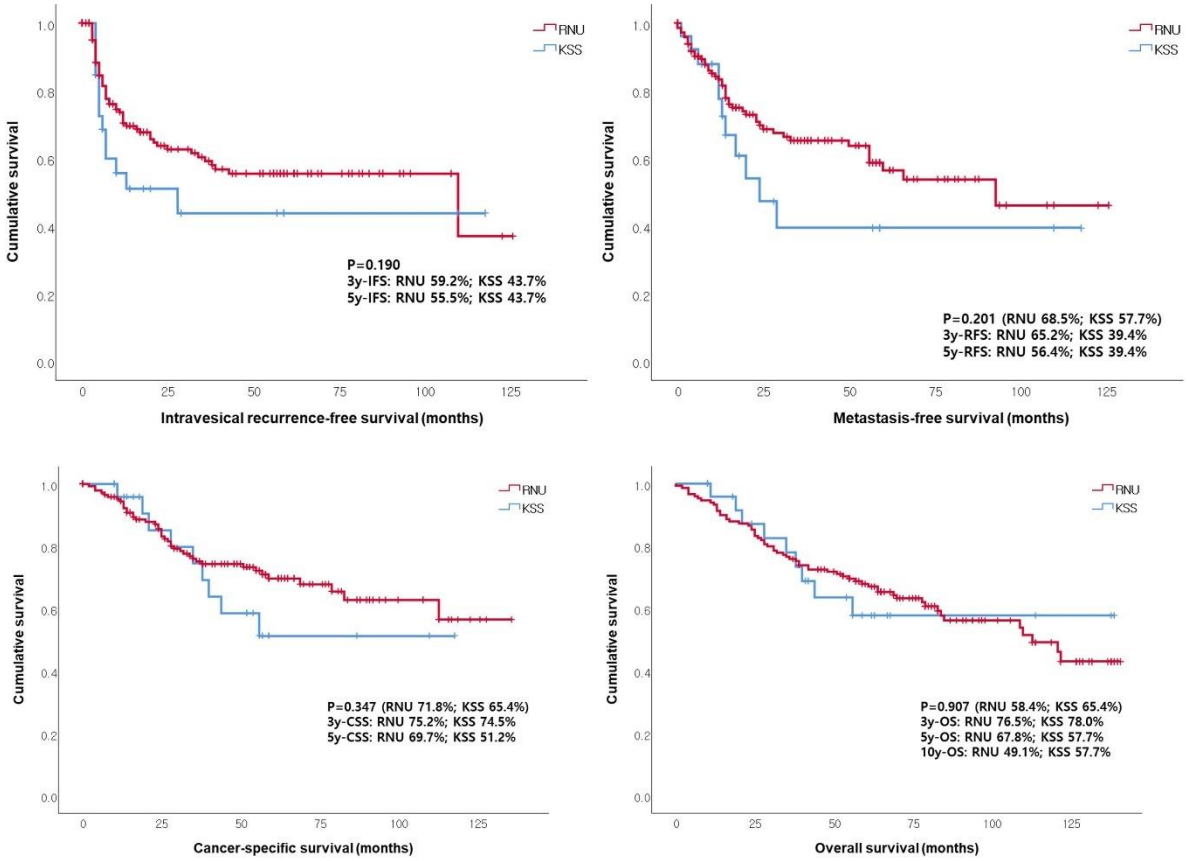


Figure 6. Survival in patients with large (≥2cm) unifocal ureter cancer

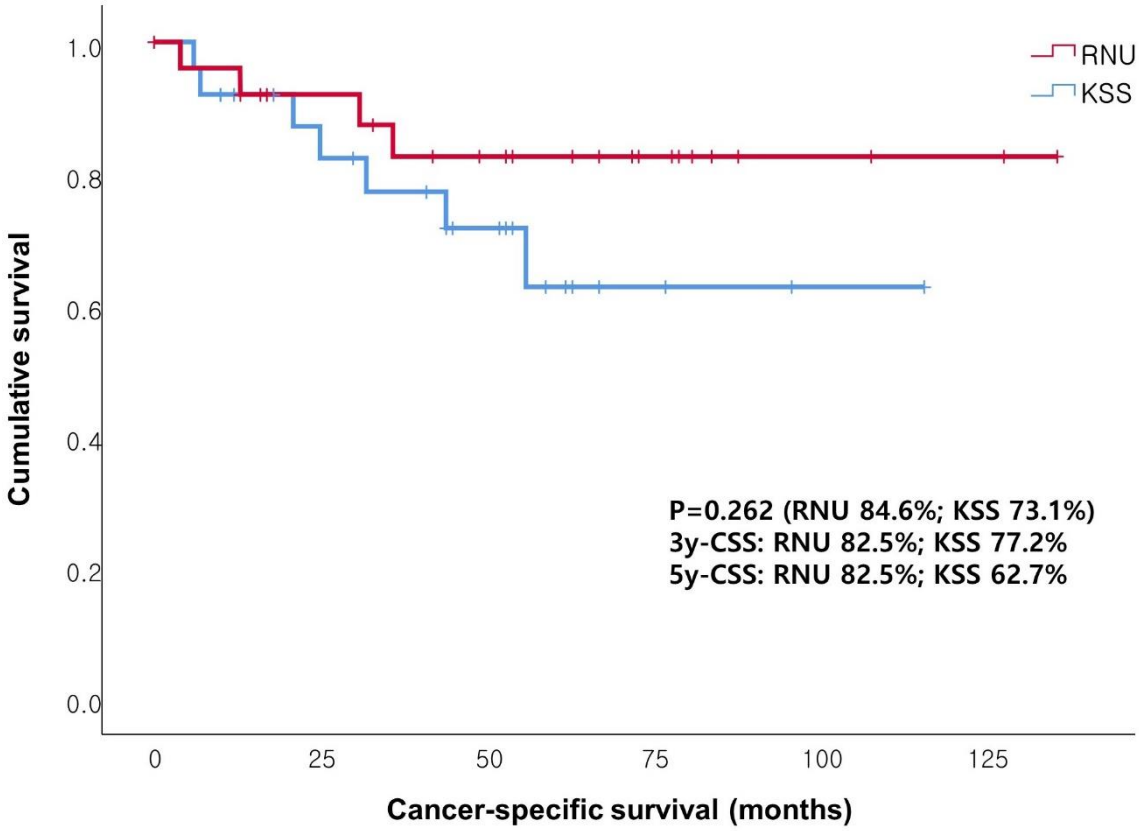


Figure 7. CSS in patients with large (≥2cm) unifocal ureter cancer after propensity score matching

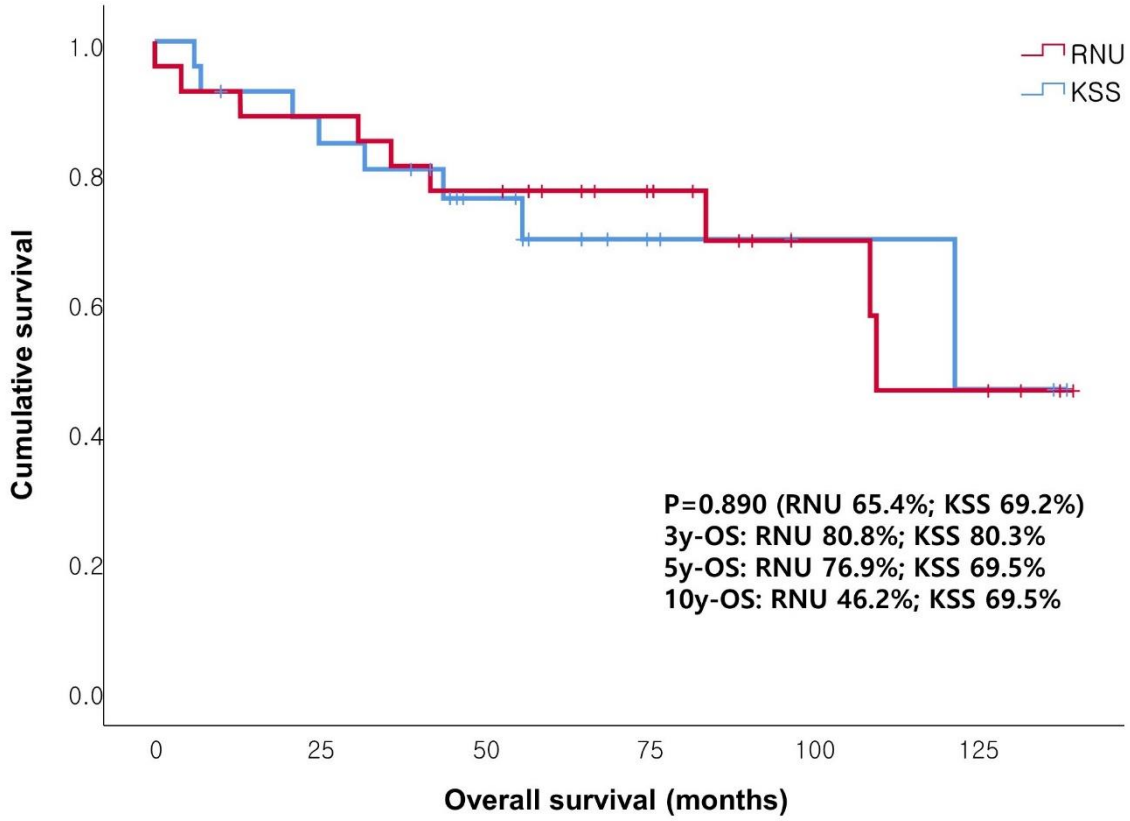


Figure 8. OS in patients with large (≥2cm) unifocal ureter cancer after propensity score matching

Renal functional loss and clinical aftermath after RNU and KSS

In the total UTUC cohort of 708 patients, Table 14 shows a statistically significant reduction in eGFR within the RNU group (−14.5 ± 17.6 mL/min/1.73 m^2) compared to the KSS group (2.4 ± 9.3 mL/min/1.73 m^2; P 〈0.000).

In the total UTUC cohort of 708 patients, following RNU (N = 646), 229 patients (35.4%) exhibited a post−surgery eGFR 〈50 mL/min/1.73 m^2, among whom 105 (16.3%) had an advanced stage (≥pT2). In the PUC cohort of 347 patients, following RNU (N = 292), 96 patients (32.9%) exhibited a post−surgery eGFR 〈50 mL/min/1.73 m^2, among whom 47 (16.1%) had an advanced stage (≥pT2). In the UUC cohort of 269 patients, following RNU (N = 219), 70 patients (32.0%) exhibited a post−surgery eGFR 〈50 mL/min/1.73 m^2, among whom 33 (15.1%) had an advanced stage (≥pT2) (Figure 9).

In the total UTUC cohort of 708 patients, following RNU (N = 646), preoperative CRF 〈50 mL/min/1.73 m^2, as determined by 99mTc−DTPA renography, was observed in 318 patients (49.2%), among whom 149 (23.1%) had an advanced stage (≥pT2). In the PUC cohort of 347 patients, following RNU (N = 292), 136 patients (46.6%) exhibited preoperative CRF 〈50 mL/min/1.73 m^2, among whom 78 (26.7%) had an advanced stage (≥pT2). In the UUC cohort of 269 patients, following RNU (N = 219), 98 patients (44.7%) exhibited preoperative CRF 〈50 mL/min/1.73 m^2, among whom 55 (25.1%) had an advanced stage (≥pT2) (Figure 10).

In the total UTUC cohort of 708 patients, following RNU (N = 646), preoperative IRF ≥30 mL/min/1.73 m^2 was observed in 253 patients (39.2%), among whom 98 (15.2%) had an advanced stage (≥pT2). In the PUC cohort of 347 patients, following RNU (N = 292), 88 patients (30.1%) exhibited preoperative IRF ≥30 mL/min/1.73 m^2, among whom 45 (15.4%) had an advanced stage (≥pT2). In the UUC cohort of 269 patients, following RNU (N = 219), 63 patients (28.8%) exhibited preoperative IRF ≥30

mL/min/1.73 m^2, among whom 29 (13.2%) had an advanced stage (≥ pT2) (Figure 11).

Table 14. Four weeks follow-up of renal function after surgery

	Preoperative eGFR[a]	Postoperative[b] eGFR	P
Overall	67.9 ± 21.2	54.8 ± 16.5	
Surgical methods			<0.000
RNU	68.5 ± 20.6	54.0 ± 15.1	
KSS	62.0 ± 26.6	64.1 ± 25.2	
Pathologic stage			<0.000
Advanced T-stage (≥pT2)	64.4 ± 20.1	54.7 ± 16.3	
Low T-stage (≤pT1)	71.1 ± 21.7	55.0 ± 16.7	

Abbreviations: eGFR=estimated glomerular filtration rate; KSS=kidney sparing surgery; RNU=radical nephroureterectomy

[a] eGFR, mL/min/1.73m^2, mean ± SD

[b] eGFR evaluated 4 weeks after surgery

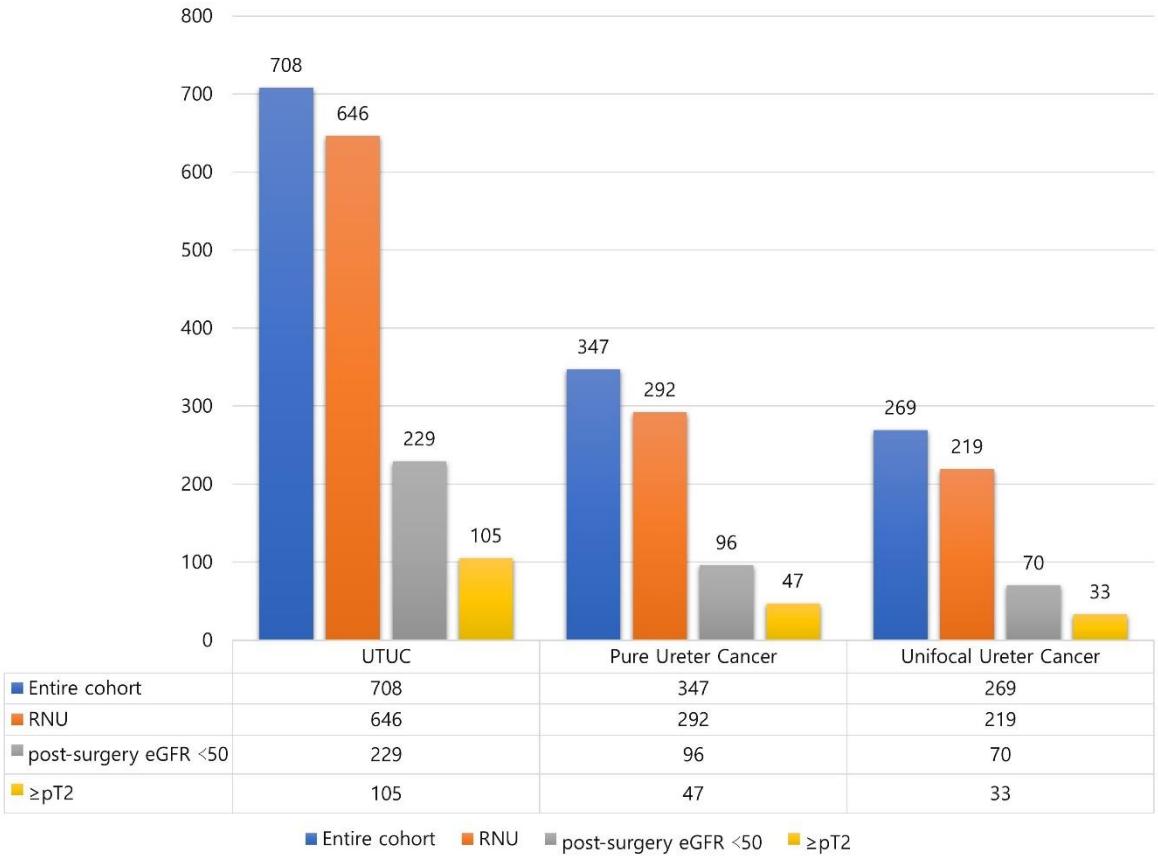


Figure 9. Distribution of patients with Post-Surgery eGFR 〈50mL/min/1.73m^2 and Advanced stage (≥pT2)

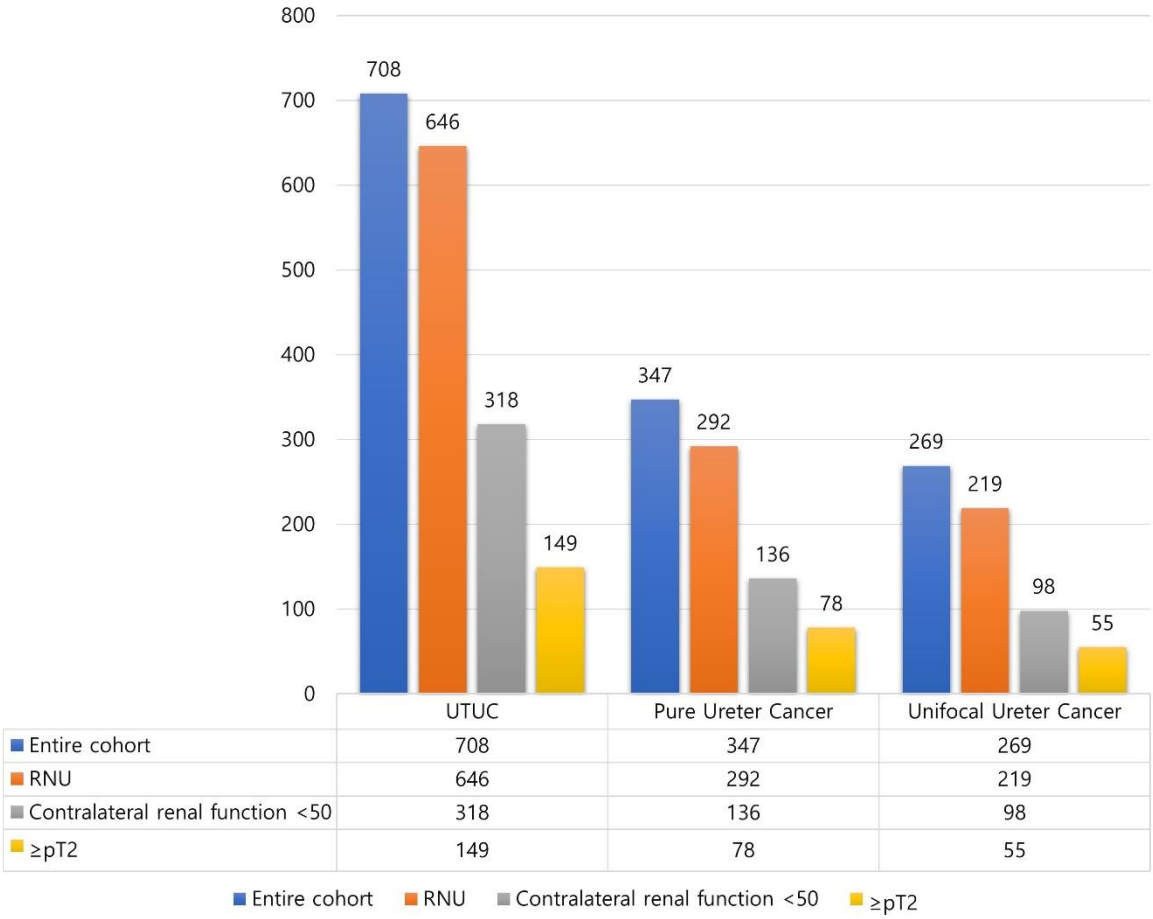
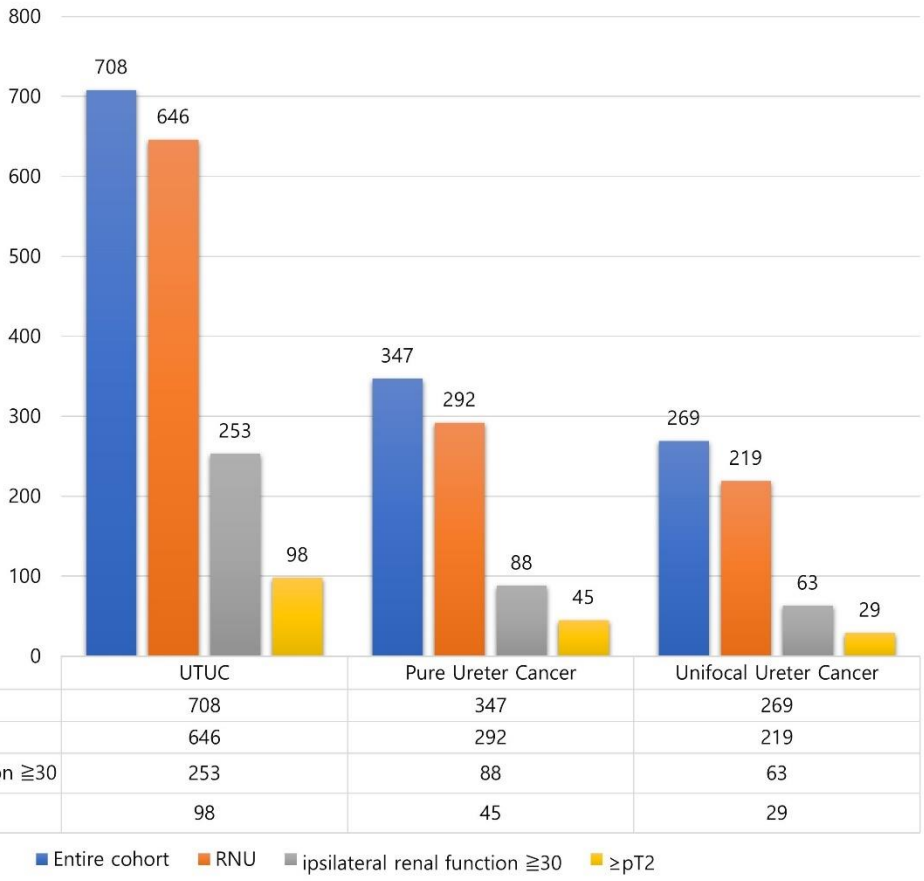


Figure 10. Distribution of patients with Contralateral split renal function 〈50mL/min/1.73m^2 and Advanced stage (≥pT2)



	UTUC	Pure Ureter Cancer	Unifocal Ureter Cancer
Entire cohort	708	347	269
RNU	646	292	219
ipsilateral renal function ≧30	253	88	63
≥pT2	98	45	29

Figure 11. Distribution of patients with Ipsilateral split renal function ≥30 mL/min/1.73m^2 and Advanced stage (≥pT2)

Functional advantage by KSS

In the entire KSS group (N = 62), there was a slight increase in postoperative eGFR (2.4 ± 9.3 mL/min/1.73 m^2). Furthermore, 40 patients (64.5%) had an eGFR ≥50 mL/min/1.73 m^2 after surgery, and among them, 10 patients (16.1%) had advanced stage (≥pT2). In practice, seven of these patients received cisplatin-based adjuvant chemotherapy.

Among the patients who underwent 99mTc-DTPA renography, seven individuals had CRF <20 mL/min/1.73 m^2, and the mean post-surgery eGFR for these patients was 39.9 mL/min/1.73 m^2, allowing them to avoid dialysis.

Surgical method for KSS

A detailed subgroup analysis was conducted on patients with UUC who underwent KSS (N = 50). KSS was performed utilizing four distinct approaches: DU (N = 29), IU (N = 13), UTA (N = 3), and UU (N = 5).

DU

The DU group consisted of patients with tumors exclusively located in the distal ureter. Among them, 11 patients (37.9%) were identified as high-grade based on preoperative ureteroscopic biopsy. The mean preoperative eGFR was 65.3 mL/min/1.73 m^2, and 17 patients (58.6%) had CRF <50 mL/min/1.73 m^2, as determined by 99mTc-DTPA renography. The average tumor size was 2.2 cm, and there were two patients with only a single kidney.

UTA

The UTA group (N = 3) utilized semi-rigid ureteroscopy to remove the tumor using a basket and performed laser ablation at the tumor base. Within this group, two patients

had tumors located in the mid-ureter, while one had a tumor in the distal ureter. Among them, two patients had small tumors (<1 cm) in size. However, one patient, with a clinically measured tumor size of 2 cm, had a preoperative eGFR of 21 mL/min/1.73 m^2.

UU

The UU group (N = 5) included patients with tumors located in the proximal ureter in three patients and the mid-ureter in two patients. All patients had preoperative eGFR <50 mL/min/1.73 m^2, with three of them having a single kidney. UU can be considered as a limited option for patients with CKD where more invasive surgeries such as IU are challenging.

IU

There were 13 patients who underwent IU, with five of them having a single kidney. This group consisted of four patients with tumors located in the proximal ureter and eight in the mid-ureter and one in the distal ureter. Nine of them had tumors measuring 2 cm or more in length. All seven patients underwent 99mTc-DTPA renography and had CRF <50 mL/min/1.73 m^2. There were four patients identified as clinically high-grade tumors through ureteroscopic biopsy, of which two had a single kidney, and two had CRF <50 mL/min/1.73 m^2. Five patients had clinically low-grade tumors. IU was primarily performed in patients with clinically low-grade tumors located in the proximal or mid-ureter with CRF <50 mL/min/1.73 m^2. However, in cases of clinically high-grade tumors located in the proximal or mid-ureter, IU was also considered for patients with a single kidney or CRF <50 mL/min/1.73 m^2.

Survival

When comparing the CSS rates among patients who underwent four different approaches for KSS, it was found that the survival rate for the UU was significantly lower (P <0.000; Figure 12). However, there was no statistically significant difference in CSS

between the DU and IU (P = 0.522; Figure 13).

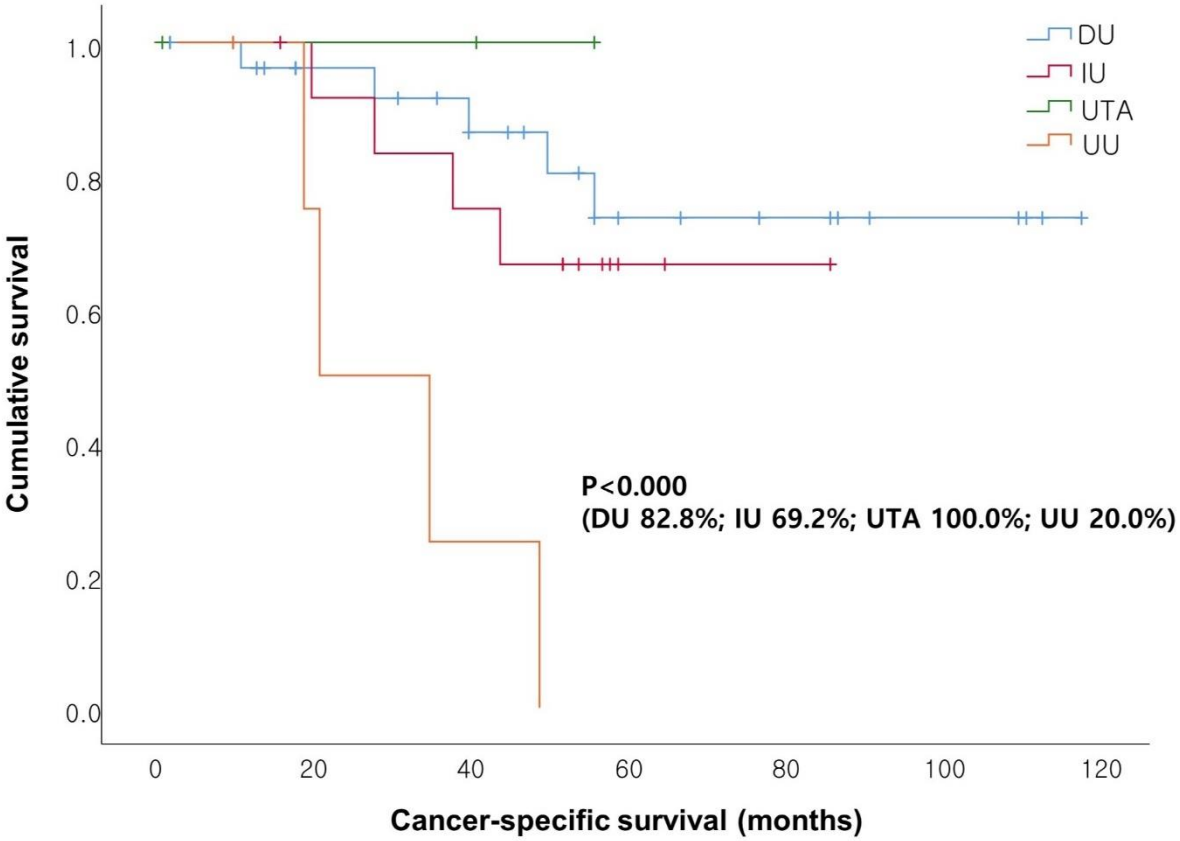


Figure 12. CSS in patients with unifocal ureter cancer who underwent four approaches of KSS

Abbreviations: DU=distal ureterectomy with reimplantation; IU=ileal ureter replacement; UTA=ureteroscopic tumor ablation; UU=ureterectomy with ureteroureterostomy

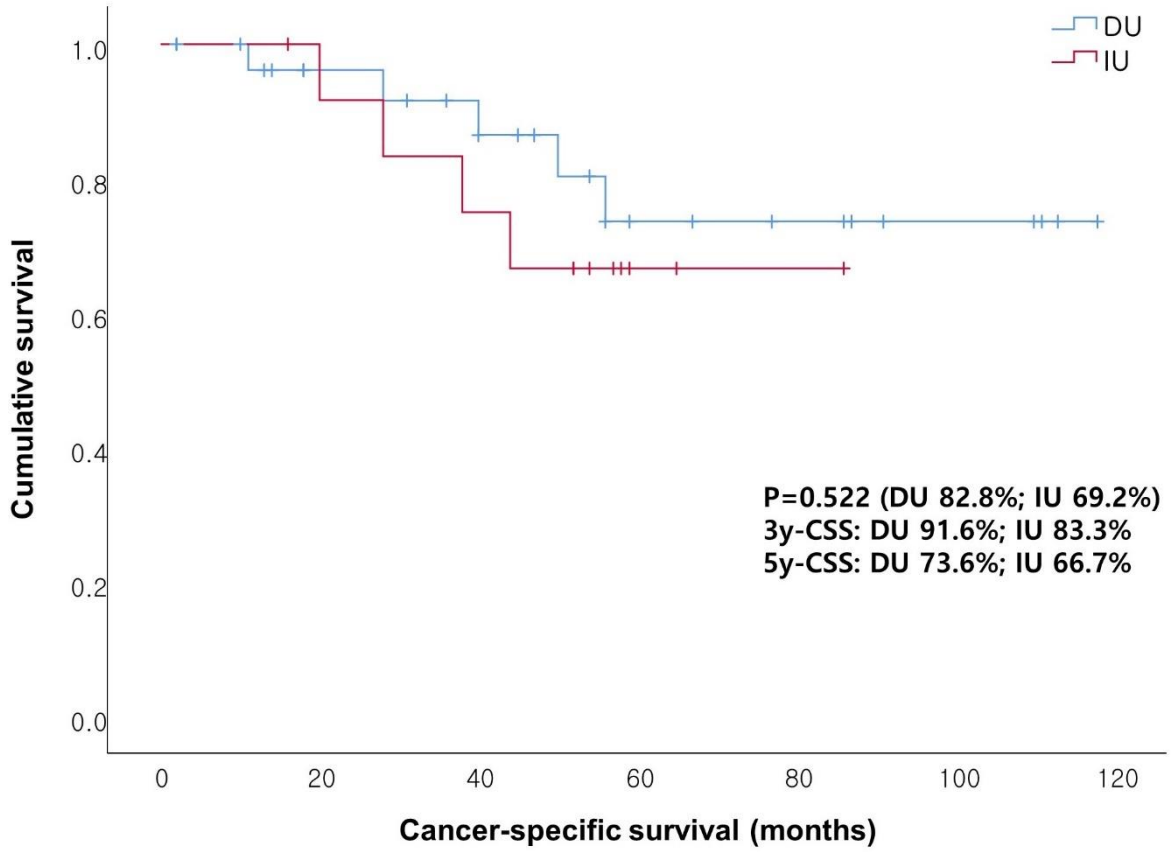


Figure 13. CSS in patients with unifocal ureter cancer who underwent DU or IU

Selecting possible candidates for KSS in ureter cancer

The decision to opt for KSS in ureter cancer was based on factors such as the presence of a single kidney, preoperative eGFR, split renal function, tumor size, tumor location, tumor grade, and tumor stage. The choice was made conservatively after thorough discussions with the patients regarding disease status and their renal function.

Figure 14 presents an advanced flowchart that should be considered when deciding between RNU and KSS for patients with ureter cancer. Applying this to the study cohort, among the patients with PUC who underwent RNU (N = 292), the number of patients with UUC, excluding those with a single kidney (N = 2), CKD stage 4 or below (N = 15), CRF ≥50 mL/min/1.73 m^2 and IRF <30 mL/min/1.73 m^2 (N = 72), was 152 (52.1%). There were 28 patients with CRF ≥50 mL/min/1.73 m^2 and IRF ≥30 mL/min/1.73 m^2, 59 patients with CRF <50 mL/min/1.73 m^2 and IRF <30 mL/min/1.73 m^2, and 35 patients with CRF <50 mL/min/1.73 m^2 and IRF ≥30 mL/min/1.73 m^2.

Among patients with UUC who received KSS (N = 50), after excluding those who had imperative KSS indications and were recommended for RNU due to a CRF ≥50 mL/min/1.73 m^2 and IRF <30 mL/min/1.73 m^2, there were 36 patients. Among these 36 patients, 25 underwent DU, eight underwent IU, and three underwent UTA. Out of 36 patients, nine (25.0%) had preoperative eGFR levels below 50 mL/min/1.73 m^2. CT scans indicated that 33 (91.7%) had non-invasive tumors, while ureteroscopic biopsy or urine cytology identified 21 (58.3%) with high-grade tumors.

Out of 36 patients, 14 had CRF <50 mL/min/1.73 m^2 and IRF <30 mL/min/1.73 m^2, comprising nine who underwent DU, three who underwent IU, and two who underwent UTA. However, all these patients successfully avoided dialysis, with post-surgery eGFR levels surpassing 30 mL/min/1.73 m^2.

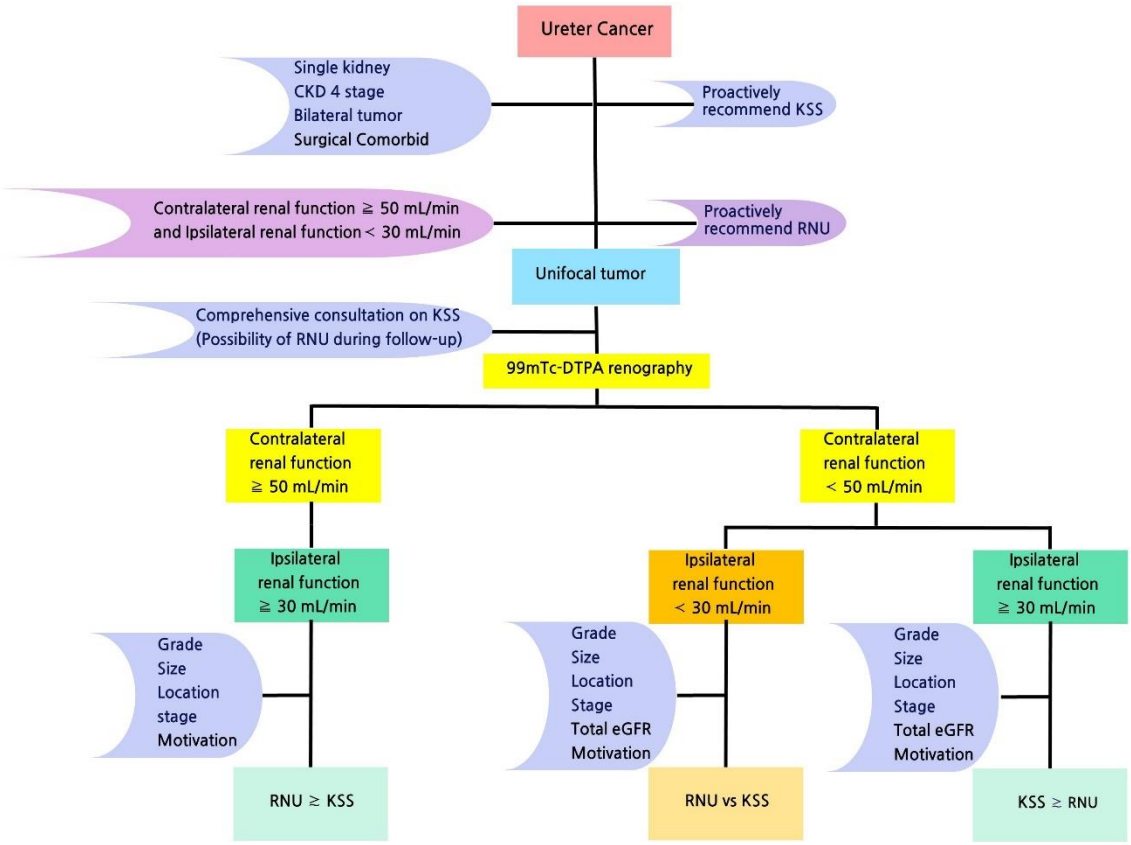


Figure 14. Flowchart of proper management of ureter cancer

DISCUSSION

Comparable survival between RNU and KSS in a cohort of 708 patients with UTUC

Comprehensive analysis of 708 patients with UTUC at the Asan Medical Center highlights the comparable survival outcomes between RNU and KSS. Strikingly, no significant differences surfaced in key metrics such as IRFS, MFS, CSS, and OS between the two surgical approaches. These findings align with a recent meta-analysis by Kawada et al. [37], cautioning against drawing definitive conclusions due to inherent biases in retrospective studies and diverse patient populations.

However, there was further nuance within my cohort. The RNU group exhibited a predisposition towards larger tumors, higher grades, advanced stages, and tumor multifocality. Despite RNU showing a lower incidence of ipsilateral kidney recurrence or disease progression [30], the analysis did not reveal a significant difference in survival between the two surgical methods due to the significant bias introduced by the higher disease severity in the RNU group.

The significance of tumor Unifocality in ≤pT1 ureter cancer

An intriguing revelation emerged concerning tumor multifocality in ≤ pT1 UTUC cases. While our analysis did not identify tumor multifocality as a significant risk factor in the overall cohort, a more focused examination of ≤pT1 UTUC cases revealed its emergence as an independent risk factor. This challenges conventional assumptions and introduces a context-dependent perspective on the prognostic implications of tumor multifocality.

This trend persisted in examination of a separate cohort with PUC. Notably, tumor

multifocality did not attain statistical significance as a risk factor in the entire PUC cohort, but it emerged as a significant factor in non-invasive (≤pT1) ureter cancer cases. This nuanced understanding of tumor multifocality underscores the need for tailored risk assessments in specific subgroups.

Novara et al. [38] discovered that tumor multifocality holds prognostic significance in patients with UTUC. In comparison to my study, Novara et al. [38] exhibited several distinctions: they reported a higher incidence of tumor multifocality; their study encompassed patients with muscle-invasive bladder cancer; and a significant proportion of their patients had concomitant CIS. However, in the study conducted by Chromecki et al. [39], tumor multifocality was not a significant risk factor in the entire UTUC cohort. Instead, it was only in the organ-confined (≤pT2) UTUC cohort that tumor multifocality was found to independently increase the risk of disease progression (HR: 1.43; p=0.019) and cancer-specific mortality (HR: 1.46; p=0.027).

Similarly to previous research, this study also identified tumor multifocality as a significant and independent risk factor in the non-invasive (≤pT1) PUC cohort. As a result, this study proceeded to analyze the survival rate and functional outcomes within the UUC subgroup.

Functional and oncological outcomes in UUC

This study has a unique focus on a relatively large population of individuals with unifocal UTUC specifically located in the ureter. Dudinec et al. [40] observed that the incidence of advanced CKD was notably lower in the cohort that underwent KSS (P=0.009), while identifying RNU as a risk factor associated with advanced CKD. In this study, similar findings were observed where the eGFR level showed a slight increase following KSS. These results align with previous research, suggesting that KSS plays a

protective role in preserving renal function.

There were no significant differences in IRFS, MFS, CSS, or OS between the RNU and KSS groups for patients with UUC which is consistent with recent research results [41–43]. Using propensity score matching to balance the discrepancies between the RNU and KSS groups, this study analyzed survival outcomes. However, no significant differences in survival rate were observed between the two surgical methods in terms of CSS and OS (as depicted in Figure 3).

According to the EAU guidelines, high-grade tumors are considered high-risk for KSS, and there is a greater risk of disease progression [14, 30]. Grasso et al. [30] reported survival rates in high-grade UTUC patients who underwent RNU as 5-year CSS of 53% and 5-year OS of 47%. In low-grade UTUC patients, they presented 5-year CSS of 89% and 5-year OS of 79%. In this study, after propensity score matching, there were no significant differences in CSS and OS between the two surgical groups. The 5-year CSS was comparable to the previous study (5-year CSS: RNU vs. KSS; 56.5% vs. 50.3%; Figure 4). Therefore, it is believed that in cases of non-invasive UUC, KSS should be considered even in high-grade UUC.

In a previous systematic review [44], it was demonstrated that a larger tumor size was significantly associated with a poorer CSS (HR = 1.66, P< 0.000) in patients with UTUC. Based on this prior research, a subgroup analysis was conducted for patients with large (≥2 cm) UUC to evaluate survival outcomes after propensity score matching. Using Keplan-Meier survival curve, there were no significant difference in CSS between RNU and KSS (p=0.262; as depicted in Figure 7). However, it is important that the average CSS rate was 84.6% for RNU and 73.1% for KSS, indicating a notable disparity. In cases of UUC where the tumor size exceeds 2cm, careful consideration should be given to the application of KSS.

Preserving renal function: Impact to clinical consequences

Comparing the impact on renal function, the statistical significance manifested in a notable decrease in eGFR within the RNU group, underscoring the potential clinical ramifications of this surgical choice.

A retrospective analysis conducted by Kaag et al. [45] revealed a mean decrease in eGFR of 24% following RNU, and more than half of the patients who initially had an eGFR above 60 mL/min/1.73m^2 experienced a postoperative drop below 60 mL/min/1.73m^2. Similarly, Raman et al. [46] reported that approximately one-quarter of all patients experienced a reduction in eGFR below 60 mL/min/1.73m^2, with roughly 15% falling below 45 mL/min/1.73m^2 after RNU. According to global statistics, CKD claims the lives of 12 million people each year [47]. Following one year of treatment, individuals undergoing dialysis face a mortality rate of 15-20%, with a five-year survival rate dropping below 50% [48].

The POUT trial demonstrated that cisplatin-based adjuvant chemotherapy provides a benefit in disease-free survival for UTUC patients with pT2 or higher stages, with renal function assessed based on eGFR ≥50 mL/min/1.73m^2 [25]. According to Galsky criteria [49], a creatinine clearance of less than 60 mL/min/1.73m^2 is not suitable for cisplatin chemotherapy. For these reasons, anticipating an eGFR below 50 mL/min/1.73m^2 and clinically invasive (≥cT2) tumor is an important factor in the treatment of UTUC.

In this study, out of the entire cohort of 646 patients who underwent RNU, 105 patients (16.3%) were confirmed to have an advanced stage (≥pT2) and post-surgery eGFR <50 mL/min/1.73m^2, while 149 patients (23.1%) were confirmed to have an advanced stage (≥pT2) and contralateral renal function <50 mL/min/1.73m^2. Post-surgery eGFR measurements were determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which estimates GFR based on creatinine clearance

[50]. Since it relies on serum creatinine produced within the body, this method typically yields higher values compared to renal function assessed by 99mTc-DTPA renography [51]. As a result, there is a discrepancy between the post-surgery eGFR estimated using serum creatinine and the contralateral renal function assessed by 99mTc-DTPA renography, which may affect the eligibility of more patients for cisplatin-based chemotherapy after RNU.

Optimal approaches for UUC: A consideration of KSS methods

Exploration of optimal approaches for UUC encompasses a range of surgical techniques, each tailored to specific clinical scenarios. DU emerges as a compelling option for clinically high-grade tumors in the distal ureter [52]. However, its feasibility may be compromised in patients with recurrent bladder cancer or challenges in maintaining tension-free ureteroneocystostomy [53].

IU comes to the forefront as a viable technique for tumors localized in the proximal or mid-ureter. Particularly pertinent in cases involving high-grade tumors or patients with a single kidney or CKD, IU offers a conservative approach with potential benefits [31].

The selection of UTA, while limited by challenges in achieving complete tumor removal and obtaining precise pathology results, remains a consideration for smaller-sized tumors with anticipated low-grade characteristics [54].

UU, while an option in patients who cannot endure more invasive procedures involving bowel resection, comes with a cautionary note regarding its less favorable prognosis. The comprehensive exploration of these surgical techniques underscores the need for personalized strategies, considering the intricacies of each case [43].

Identifying suitable candidates for KSS in ureter cancer: Clinical considerations

This study advocates for a nuanced approach in identifying suitable candidates for KSS, emphasizing clinical considerations that extend beyond the tumor itself. The presented flowchart for the management of ureter cancer encapsulates imperative indications for KSS, such as only having a single kidney, CKD stage 4, bilateral tumors, and surgical comorbidities. CKD stage 4, defined by an eGFR of 15–29 mL/min/1.73 m^2 [55], emerges as a crucial criterion, given its implications for postoperative dialysis and eligibility for carboplatin chemotherapy [56].

The Galsky definition [49] stipulates a requirement of renal function ≥60 mL/min/1.73 m^2 for the use of cisplatin, but United Kingdom oncologists commonly practice using cisplatin with an eGFR of ≥50 mL/min/1.73 m^2 [25]. For these reasons, when CRF is ≥50 mL/min/1.73 m^2 and IRF is <30 mL/min/1.73 m^2, RNU is strongly recommended.

If CRF is <50 mL/min/1.73m^2 and IRF is ≥30 mL/min/1.73m^2, there is a possibility of having an eGFR <50 mL/min/1.73m^2 after RNU. In this case, KSS should be a prior choice, taking into account factors such as tumor grade, size, location, stage, preoperative eGFR, and the patient's motivation for renal preservation.

The interplay between CRF and IRF, tumor characteristics, and patient preferences unfolds as pivotal factors in decision-making. Notably, considerations around eligibility for cisplatin-based chemotherapy add an additional layer of complexity to the decision-making process. This study provides a framework for navigating these complexities, offering guidance for clinicians in tailoring their approach based on individual patient profiles.

Limitations

While our study provides valuable insights, certain limitations must be acknowledged. The retrospective nature of the study, coupled with its single-center design, raises questions about the generalizability of the findings to broader patient populations. Selection biases, inherent in the non-randomized decision-making process for RNU or KSS, introduce confounding factors, impacting the internal validity of the study.

Of the ten patients who underwent UTA, each was found to have a final pathological stage of pTa. Nonetheless, the reliability of this pathology poses an undeniable limitation to this study, underscoring the need for future research dedicated to achieving a more precise staging process.

The relatively short follow-up period represents a constraint on the comprehensive evaluation of long-term outcomes. This limitation underscores the need for extended research, potentially incorporating multicenter studies and longer follow-up durations to substantiate my findings.

CONCLUSIONS

For ureter cancer patients with single kidneys, CKD stage 4 or below, bilateral tumors, or high surgical morbidity, KSS is the initial recommendation. When CRF is ≥50 mL/min/1.73 m^2 and IRF is <30 mL/min/1.73 m^2, RNU is proactive. If CRF is <50 mL/min/1.73 m^2 and IRF is ≥30 mL/min/1.73 m^2, KSS should be recommended to enhance the likelihood of adjuvant chemotherapy. The decision between RNU and KSS should take into consideration tumor characteristics, clinical staging, and patient preferences for kidney preservation.

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KOREAN ABSTRACT

서론

요관암은 신우암과 다르게 다양한 신장보존수술 옵션을 고려해야 하는 독특한 특징이 있다. 현재의 지침은 신기능에 대한 고려가 부족하며, 주로 질병 위험을 기반으로 하고 있으며, 신우암과 요관암을 구분하지 않고 있다. 본 연구에서는 요관암 환자들의 적절한 치료 지침을 제시하기 위해 근치적 신장요관절제술을 받은 환자와 신장보존수술을 받은 환자 간의 생존률과 신기능의 변화를 비교하였다.

대상 및 방법

2011년부터 2019년까지 서울아산병원에서 수술적 치료를 받은 708명의 상부요로상피암 환자 중 646명이 근치적 신장요관절제술을 받았으며 62명이 신장보존수술를 받았다. 후향적 분석을 통해 비침윤성 상부요로상피암에서 종양의 단일 발생이 중요한 예후 인자로 분석되었다. 이에 따라 하위 그룹 분석에서는 단일 발생 요관암에 중점을 두어 근치적 신장요관절제술과 신장보존수술 간의 신기능 및 생존률을 분석하였다. 궁극적으로 근치적 신장요관절제술을 시행한 요관암 환자 중 잠재적인 신장보존수술 후보자를 식별하고자 했다.

결과

상부요로상피암에서 근치적 신장요관절제술과 신장보존수술 그룹 간에는 방광 내 재발율, 전이 생존율, 암 특이적 생존율 또는 전체 생존율에서 유의한 차이가 발견되지 않았다. 비침윤성 상부요로상피암 하위 그룹에서 종양 다발성은 암 특이적 생존율에 독립적인 위험 인자로 나타났으며 (위험도 = 2.221, 95% 신뢰도: 1.231-4.010, P = 0.008), 비침윤성 순수 요관암 하위 그룹에서도 종양 다발성이 중요한 위험 인자로 확인되었다 (위험도 = 2.627, 95%

신뢰도: 1.305-5.980, P = 0.019).

단일 발생 요관암 하위 그룹에서 근치적 신장요관절제술 그룹의 평균 사구체 여과율은 감소하였고 (-11.2 ± 17.8 mL/min/1.73 m^2), 반면 신장보존수술 그룹에서는 약간의 증가를 보였다 (3.1 ± 7.9 mL/min/1.73 m2; P 〈0.000). 단일 발생 요관암 하위 그룹을 근치적 신장요관절제술 (50명) 및 신장보존수술 (50명) 그룹으로 1:1 매칭한 후에도 두 가지 수술 방법 간에 생존율에서 유의한 차이가 없었다.

근치적 신장요관절제술을 받은 순수 요관암 환자 (292명) 중에서 단일 신장을 가진 환자 (2명), 만성신부전 4단계 이하 환자 (15명), 대측 신기능 50 mL/min/1.73 m^2 이상이며 동측 신기능 30 mL/min/1.73 m^2 미만인 환자 (72명)를 제외한 단일 발생 요관암 환자의 수는 152명 (52.1%) 이었다. 대측 신기능 50 mL/min/1.73 m^2 이상이며 동측 신기능 30 mL/min/1.73 m^2 이상인 환자는 28명, 대측 신기능 50 mL/min/1.73 m^2 미만이며 동측 신기능 30 mL/min/1.73 m^2 미만인 환자는 59명, 대측 신기능 50 mL/min/1.73 m^2 미만이며 동측 신기능 30 mL/min/1.73 m^2 이상인 환자는 환자는 35명이었다.

결론

요관암에서 단일 신장, 만성신부전 4단계 이하, 양측 종양, 수술 후 합병증이 심할 것으로 예상되는 환자에게는 신장보존수술을 먼저 권유하여야 한다. 대측 신기능이 50 mL/min/1.73 m^2 이상이고 동측 신기능이 30 mL/min/1.73 m^2 미만인 경우 근치적 신장요관절제술이 적극 권고되어야 한다. 대측 신기능이 50 mL/min/1.73 m^2 미만이고 동측 신기능이 30 mL/min/1.73 m^2 이상인 경우 신장보존수술이 보조 항암화학요법의 가능성을 높일 수 있기 때문에 적극 권유되어야 한다. 요관암에서 근치적 신장요관절제술과 신장보존수술은 신기능에 기초하여 종양의 특성, 임상적 병기, 신장 보존을 위한 환자의 선호도를 고려하여 결정되어야 한다.