

ARTICLE



Operative management in patients with upper tract urothelial carcinoma in Iceland: a population-based study

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ABSTRACT

Objective: Radical nephroureterectomy is the standard treatment of organ-confined upper tract urothelial carcinoma (UTUC). The objective of this study was to investigate survival and bladder recurrence rate in Icelandic patients with UTUC who underwent radical nephroureterectomy (RNU) or other procedures with curative intent.

Material and methods: All patients who were diagnosed with UTUC in Iceland from 2003 to 2016 and treated with curative intent were included in the study. Information on patients was obtained retrospectively from patients' medical records and from the Icelandic Cause of Death Registry.

Results: Overall 63 patients underwent a procedure for UTUC with curative intent in Iceland during the study period. The median age was 71 years and the majority were male (65%). In 50 patients (79%), the tumor was a primary UTUC. The most common procedure was RNU (78%) and eight patients (13%) underwent a kidney-sparing procedure. No patient died within 90 d of surgery. Twenty-eight patients (44%) had pathological stage T2 or higher, whereas 35 patients (56%) had pathological stage T1 or lower. The median follow-up time was 98.8 months. During the follow-up time 25 patients (40%) were diagnosed with recurrence in the bladder. Five-year cancer-specific survival (CSS) was 67%.

Conclusions: This population-based study shows that the oncologic outcome in Icelandic patients with UTUC is similar to what has been reported in other countries. Bladder recurrence rate is high and can hopefully be reduced by improvements in surgical and intravesical instillation treatment. Possibly more kidney-sparing surgeries could have been done during the study period; however, careful selection for those procedures is mandatory.

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Introduction

Upper tract urothelial carcinoma (UTUC) is much less common than bladder cancer. UTUC accounts for 5–10% of all urothelial carcinomas and its incidence is approximately two cases a year per 100,000 inhabitants in western countries [1]. UTUC tumors are invasive at diagnosis in 50–60% of cases compared to 15–25% of bladder tumors, resulting in a generally worse prognosis in patients with UTUC [2]. Radical nephroureterectomy (RNU) with bladder cuff excision is considered the gold standard in treatment of organ-confined UTUC. However, studies have shown that kidney-sparing surgery (KSS) results in a similar oncologic outcome compared to RNU in low-risk tumors [3]. Long-term survival of patients with UTUC varies greatly between tumor stages. Patients with low-stage tumors have five-year survival rates as high as 90%, but five-year survival rates for patients with high-stage tumors or regional lymph node metastasis is under 50% [2].

The main aim of this study was to investigate survival in Icelandic patients with UTUC who are treated with RNU or some other procedure with curative intent. We also wanted

to investigate bladder recurrence rate, operative morbidity and mortality of patients following operative management of UTUC in Iceland.

Material and methods

This study is a retrospective population-based study including all patients diagnosed with UTUC who underwent surgical treatment with curative intent from 2003 to the end of 2016. The surgeries were performed at two hospitals, Landspítali University Hospital (LUH) in Reykjavík and Akureyri Hospital. Patients were identified by obtaining a list from the Icelandic Cancer Registry for specific ICD-10 number codes (C65 and C66). All patients who had a metastatic disease or did not undergo an operation with curative intent were excluded. Information on patients was obtained from patients' medical records and the Iceland Cause of Death Registry. One pathologist reviewed all cases where tumor grade was originally recorded according to the 1973 WHO grading system [4] and evaluated the samples according to the 2004/2016 WHO grading system [5]. Perioperative mortality was defined as death from a complication of the procedure within 90 days of procedure. The following variables were recorded:

Table 1. Clinical characteristics of patients who underwent operative management of UTUC in Iceland with curative intent between 2003 and 2016.

No. of patients	63
Male	41 (65)
Female	22 (35)
Age (years)	
Median (IQR)	71 (64.5–77.5)
ASA score	
1	4 (6)
2	34 (54)
3	20 (32)
4	3 (5)
NA	2 (3)
Presenting symptoms ^a	
Hematuria	49 (78)
Flank pain	15 (24)
Fatigue	2 (3)
Incidental	5 (8)
Previous history of bladder cancer	13 (21)
Tumor location	
Renal pelvis	29 (46)
Ureter	27 (43)
Renal pelvis and ureter	7 (11)
Concomitant bladder cancer	9 (14)
Diagnostic ureteroscopy	44 (70)

IQR: Interquartile range. Data is shown as number of patients (%) unless otherwise indicated.

^aPatients presenting with more than one symptom are counted more than once.

gender, age, American Society of Anesthesiology score (ASA perioperative classification), clinical and pathological TNM-classification of malignant tumors (TNM), tumor grade according to 2004/2016 WHO grading system, surgeon, previous history of bladder cancer, perioperative blood loss (ml lost during procedure), operation time, length of hospital stay, unexpected readmission within 90 days after surgery, complications, follow-up time, bladder recurrence or metastasis, day of death and cause of death. Information on cause of death was obtained from the Iceland Cause of Death Registry. Complications were recorded according to the Clavien–Dindo classification system. All complications up to 90 days after surgery were recorded. Major complications were defined as Clavien grade 3–5 and minor complications as Clavien grade 1–2.

Statistical analysis

All statistical analysis was done using the R version 3.0.2 software (R Foundation for Statistical Computing, Vienna, Austria). Differences between groups of patients in distributions for categorical variables were tested with Fisher-exact tests and a chi-squared test. A two-sided t-test and a *post-hoc* analysis with Bonferroni adjustment were used to evaluate differences between groups in length of stay at hospital as well as linear regression analysis. Survival analysis was used to analyze long-term survival of patients. The Kaplan–Meier method was used in the survival analysis as well as a Cox regression analysis model to calculate differences between groups and hazard ratios. Statistical significance was set at $p < .05$.

Results

Patient characteristics

Overall, 63 patients underwent a procedure in curative intent for UTUC in Iceland during the 14-year study period. During

Table 2. Intraoperative data for patients with UTUC in Iceland who underwent operative management with curative intent in 2003–2016.

Type of procedure	
Radical nephroureterectomy	49 (78)
Nephrectomy	6 (9)
Distal ureterectomy with Boari flap	5 (8)
Endoscopic resection	3 (5)
Operative approach ^a	
Open	34 (69)
Laparoscopic	11 (22)
Robot-assisted	4 (8)
Bladder cuff excision ^a	34 (69)
Operation time (minutes) ^{a,b}	
Mean (SD)	159 (63)
Estimated blood loss (ml) ^{a,c}	
Mean (SD)	451 (334)

Data is shown in number of patients (%) unless otherwise indicated.

^aOnly patients who underwent RN are included.

^bData on 12 patients were missing.

^cData on 13 patients were missing.

the study period 82 patients were diagnosed with UTUC in Iceland; eight had metastatic disease and were excluded and 11 patients had a non-metastatic disease but did not receive curative treatment because of other factors, such as old age and comorbidities, and were therefore excluded from the study.

The median age of patients was 71 years and the majority were male (65%). Renal pelvic tumors were slightly more common than tumors in the ureter (Table 1). Thirteen patients (21%) had a previous history of bladder cancer and nine patients (14%) had concomitant bladder cancer. The bladder cancer was non-muscle invasive in all patients that had concomitant bladder cancer.

The procedures were performed at two institutions during the study period, however, the vast majority was performed at LUH. Only eight procedures (13%) were performed at Akureyri Hospital during the 14-year study period and six of those were RNUs.

Intraoperative data are presented in Table 2. Forty-nine patients (78%) underwent a RNU in the study cohort and an open surgery was the most common approach (69%). A bladder cuff excision was performed on 34 patients (69%) of those who underwent a RNU. KSS was performed on eight patients (13%), three patients (5%) underwent an endoscopic resection and five patients (8%) underwent a distal ureterectomy with a Boari flap reconstruction.

The median length of stay at hospital was 7 days (IQR: 5). When we look at only the patients who underwent a RNU the mean length of stay at hospital is also 7 days (IQR: 5). Length of stay shortened over the study period by 0.5 d per year on average ($p < .01$). We divided the study period evenly into three groups according to the time of procedure. In group 1 were patients who underwent the procedure between 2003 and the end of 2007, in group 2 were patients who underwent the procedure between 2008 and the end of 2013, and in group 3 were patients who underwent the procedure between 2013 and the end of 2016. The median length of stay was 9 (IQR: 5), 7 (IQR: 4) and 5.5 d (IQR: 4.25) in group 1, 2 and 3, respectively. Patients who were operated on between 2013 and the end of 2016 had a significantly shorter hospital stay compared to groups 1 and 2 (Figure 1). When looking at the length of stay at hospital

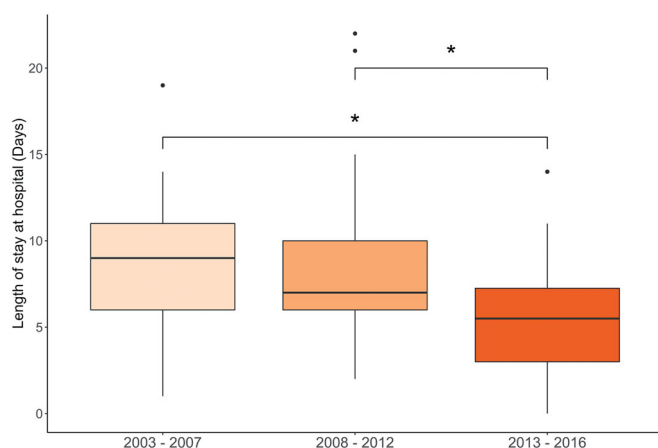


Figure 1. Boxplot demonstrating length of stay at hospital for patients who underwent operative management for UTUC with curative intent in Iceland in 2003–2016, stratified by date of operation.

Table 3. Pathological tumor and nodal stages of patients with UTUC who underwent an operative management with curative intent in Iceland in 2003–2016.

	No. of patients
T stage	
pTa	29 (46)
pTis	2 (3)
pT1	4 (6)
pT2	9 (14)
pT3	14 (22)
pT4	5 (8)
N stage	
pN0	57 (90)
pN+	6 (10)
Grade	
Low	21 (33)
High	42 (67)

Data is shown as number of patients (%).

stratified by operation technique we found that patients who underwent a robot-assisted surgery had a significantly shorter length of stay at hospital compared to patients who underwent an open procedure, with a median length of stay of 3 days (IQR: 1) and 8 days (IQR:5), respectively ($p = .025$). No other differences between groups were found. There were no readmissions to hospital within 90 days of surgery. No patient died within 90 days of surgery.

Pathologic tumor and nodal stages are outlined in Table 3. Twenty-eight patients (44%) had pathological stage T2 or higher, whereas 35 patients (56%) had pathological stage T1 or lower. Six patients (10%) had lymph node-positive disease. Four patients (6%) received adjuvant chemotherapy and one patient (2%) received adjuvant radiation therapy.

Complications

A total of eight complications were recorded in four patients (6%) up to 90 d after surgery. The most common complication was pneumonia (5%). One patient (2%) was diagnosed with a ureterocutaneous fistula after a distal ureterectomy, which was treated with a nephrostomy tube (Table 4).

Table 4. Complications after operative management for UTUC in Iceland in 2003–2017 summarized according to type and stratified by Clavien grade.

Type of complication	Clavien-Dindo grade ^a		
	1–5	1–2	3–5
Cardiovascular			
Myocardial infarction	1 (2)	0 (0)	1 (2)
Acute heart failure	1 (2)	0 (0)	1 (2)
Infectious			
Pneumonia	3 (5)	3 (5)	0 (0)
Pulmonary			
Pneumothorax	1 (2)	1 (2)	0 (0)
Pleural effusion	1 (2)	0 (0)	1 (2)
Urinary tract			
Ureterocutaneous fistula	1 (2)	0 (0)	1 (2)

Data is shown as number of patients (%).

^aPatients experiencing multiple complications are counted more than once.

Survival and recurrence rate

The median follow-up time of patients was 98.8 months (IQR: 59.7 – 128.6 months). During the follow-up time 25 patients (40%) were diagnosed with a bladder recurrence and the median time from procedure to diagnosis of bladder recurrence was 8.7 months (range: 3 – 71.4 months). Bladder recurrence-free survival (BRFS) was 67% at 2 years after surgery and 61% at 5 years after surgery (Figure 1). No significant difference was found in the bladder recurrence rate between patients who underwent a diagnostic ureteroscopy compared to those who did not. Bladder cuff excision was not performed on 15 patients (31%) treated with RNU and recurrence in the residual ureter stump was diagnosed in three of those patients (20%) during the follow-up time. All patients with stump recurrences underwent an open RNU at the same institution; however, we did not find any significant predictor of recurrence in the residual ureter stump on statistical analysis.

A total of 31 patients (49%) died during the follow-up time. The vast majority of deaths (71%) were attributed to UTUC. Figure 2 demonstrates a Kaplan–Meier plot of cancer-specific survival (CSS) for patients who underwent an operative management of UTUC with curative intent in Iceland during the study period. Five-year CSS was 67%. Patients were stratified into two groups according to their T-stage and whether they had a muscle-invasive tumor or not; group 1 included patients with stage Ta, Tis and T1 and group 2 included patients with stage T2 or higher. CSS was significantly better in patients with non-muscle invasive disease compared to patients with muscle-invasive disease, with 5-year CSS of 85% and 45%, respectively (hazard ratio for group 2: 3.8; 95% CI: 1.53 – 9.44; p : .004) (Figures 3 and 4).

Discussion

This study describes the surgical management of UTUC in Iceland over a 14-year period. UTUC is a rare disease and therefore studies and publications are limited. Only one study has been published on UTUC in Iceland for the past three decades [6]. In this study emphasis was put on surgical management while Guðbjartsson et al. reported survival of all patients with UTUC, independent of TNM-stage or treatment modality, thus making any comparison difficult.

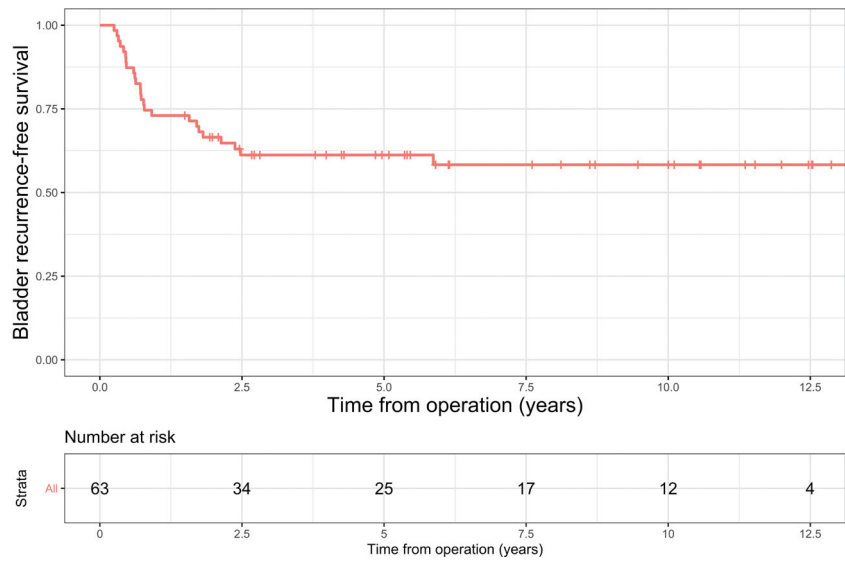


Figure 2. Kaplan–Meier plot of bladder recurrence-free survival in patients who underwent operative management for UTUC with curative intent in Iceland in 2003–2016.

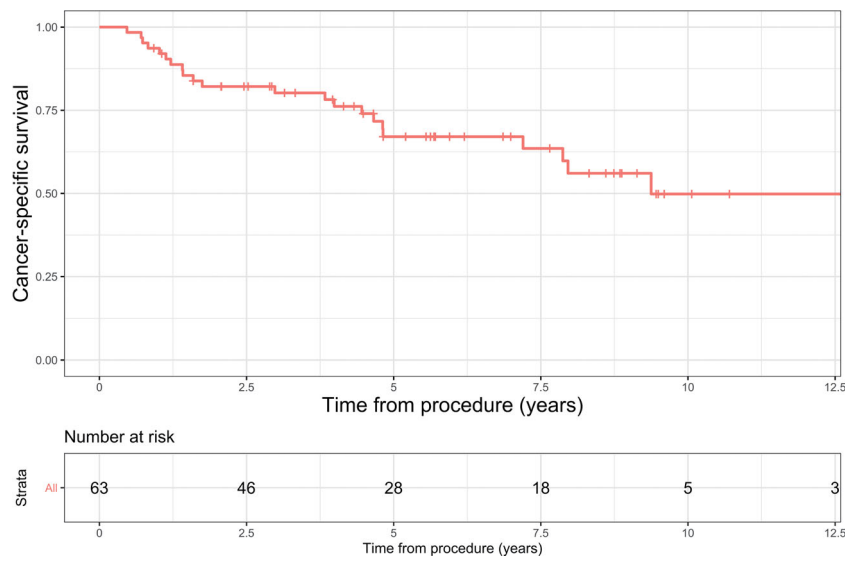


Figure 3. Kaplan–Meier plot of cancer-specific survival in patients who underwent operative management for UTUC with curative intent in Iceland in 2003–2016.

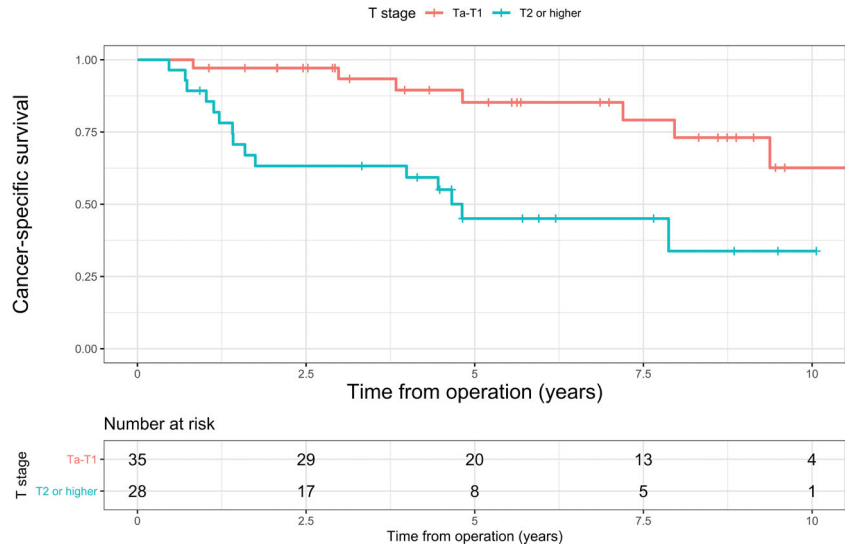


Figure 4. Kaplan–Meier plot of cancer-specific survival in patients who underwent operative management for UTUC with curative intent in Iceland in 2003–2016, stratified by tumor stage.

The long-term survival rate among patients with UTUC is known to be highly dependant on tumor grade and stage [7–9]. In this study, there is a marked difference in CSS between patients with a T2 stage tumor or higher compared to patients with T1 tumor or lower, as would be expected (Figure 2). The 5-year CSS in this study was 67%. Similar results have been described by Rouprêt et al. in a large multi-center study where CSS after nephroureterectomy for those with UTUC at 5 years was 73% [10]. Rouprêt et al. described survival after nephroureterectomy, whereas in this study survival is reported for patients undergoing nephroureterectomy and KSS. However, studies have shown that CSS of UTUC patients treated with RNU *versus* KSS is similar [3]. It has also been demonstrated that KSS results in a similar or even better overall survival compared to RNU when treating low stage and low grade tumors, most likely because it saves renal function while resulting in a similar oncologic outcome [11]. During the 14-year study period only eight kidney-sparing procedures (13%) were performed. That can be considered a fairly low number since 18 patients (29%) had a low grade and Ta stage tumor in this study. The most likely reason for this is that firstly the evidence of clinical guidelines for KSS in the treatment of UTUC was not as strong 15 years ago as it is today. Second, because of the low volume in Iceland, there are too few cases for surgeons to get the appropriate training in the complex endourologic procedures that may be required.

The number of patients with tumor stage pT3 is quite high in this study (22%). A recent population-based study in Denmark reported only 13% of pT3 tumors and 3% of pT4 tumors [12]. There is a possibility that the reason for this high number of pT3 tumors is diagnostic delay. Unfortunately, we did not have information on when symptoms started. The reason for that is the fact that this is a retrospective study and there was lack of recording data in patients' medical journals. Therefore, we do not know if there was a diagnostic delay. Another possible reason for this high percentage of pT3 tumor is that with a population as small as in this study the variability in results is high and it is likely that this difference is not statistically significant.

The in-hospital length of stay shortened significantly over the study period. Presumably the reason for this is multifactorial. When looking at length of stay stratified by operative technique we see that patients undergoing open procedures had a longer hospital stay compared to patients undergoing robot-assisted surgery. All of the robot-assisted surgeries in this study were performed in the last 3 years of the study period. We believe that the introduction of novel surgical techniques is probably one of the bigger factors lowering the length of stay in this study. There were no readmissions within 90 d of operation in this study, so this reduction in length of stay did not result in higher readmission rates.

Bladder recurrence after nephroureterectomy is well documented in the literature and studies have shown that approximately 20–50% of patients with UTUC will develop bladder recurrence after nephroureterectomy. In this study, the bladder recurrence rate was 40%, which is within that range but was higher than anticipated by the authors.

Recent studies on the recurrence rate after single bladder instillation therapy after RNU have reported a figure as low as 17%. These studies show that the relative risk reduction for bladder recurrence by applying intravesical instillation therapy is approximately 40% [13–15]. When we look at the BRFs in this study we see that most recurrences occur early after surgery (Figure 1) and the median time from procedure to diagnosis of bladder recurrence is short (8.7 months). One of the main theories on the reason for the high incidence of bladder recurrences after nephroureterectomy suggests that there is a downstream intraluminal seeding of cancer cells from the primary tumor [16,17]. Early instillation of intravesical chemotherapy has been used to reduce bladder recurrence rate after RNU and is currently in the EAU clinical guidelines for management of UTUC [1]. Intravesical instillation therapy has never been used systematically in Iceland as a prophylactic therapy for bladder recurrence after nephroureterectomy, but that will likely change in the near future based on our results and the recent EAU guidelines [1].

Recent studies have shown that the use of diagnostic ureteroscopy preoperatively is associated with increased risk of bladder recurrence after RNU [18]. Diagnostic ureteroscopy has been the standard in diagnostic work-up for patients with suspected UTUC in Iceland throughout the years, which is reflected in the frequent use of ureteroscopy in our cohort (70%). Several other factors have been shown to be associated with increased risk of bladder recurrence after RNU, such as higher tumor stage, multifocality, ureteral tumors and concomitant carcinoma *in situ* [19–21]. In this study, we did not find any significant predictor of bladder recurrence after operative management of UTUC, most likely because of a lack of statistical power.

Nephroureterectomy is a complex procedure and since UTUC is a rare disease not many RNUs are performed yearly in Iceland. The most common procedure performed during the study period was RNU (78%). However, when we look at how many procedures were performed during the 14-year study period, only 49 RNUs were performed in two institutions. So on average only 3.5 RNUs were performed per year in Iceland during the study period. Bladder cuff excision was not performed in 31% of those who underwent a RNU which is higher than anticipated by the authors. Recurrence in the ureteric stump was seen in three patients after RNU (20%), which can be viewed as a surgical error and should be less frequent than seen in this study. These findings emphasize the importance of performing a standard RNU with a bladder cuff excision to eliminate the risk of recurrence in the residual ureteric stump. Today RNUs are only performed at one institution (LUH) in Iceland and by one surgeon, which we feel is important to maintain competence in this complex procedure.

The complication rate of 6% as seen in this study is low and it is very likely that some minor complications have been missed. It is however unlikely that major complications have been overlooked and in this study the major complication rate was 5%, which is similar to what other studies have shown, reporting major complications after nephroureterectomies to be 3–8% [22,23].

One of the limitations of this study is the lack of statistical power, i.e. only 63 patients underwent a procedure for UTUC with curative intent during the 14-year period in Iceland. This small number of cases makes any statistical analysis difficult. Another restriction is the fact that this is a retrospective study. The most likely reason for the low minor complication rate reported is that this was a retrospective study and those complications are not recorded in the patients' medical records. The strength of this study is the fact that this is a population-based study where curative management for a rare cancer is described for a whole nation.

In conclusion, this study demonstrates an acceptable operative and oncologic outcome for patients with UTUC who undergo surgical management in Iceland. Length of stay after RNU has been shortened by the introduction of novel surgical techniques. Bladder recurrences are common but can hopefully be reduced by further improvements in surgical treatment and intravesical instillation treatment. It can be debated that too few kidney-sparing surgeries were performed during the study period; however, patients should be carefully chosen for such procedures.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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