

Flexible Ureterorenoscopy for Concomitant Large-Burden Renal and Ureteral Stones is the Preferred Treatment

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RIRS; Retrograde Intrarenal Surgery; Nephroureterolithiasis; Large Renal Stones; Ureteroscopy

Abbreviations:

f-URS: Flexible Ureteroscopy; UUT= Upper Urinary Tract; PCNL= Percutaneous Nephrolithotomy; Mini-PCNL= Mini Percutaneous Nephrolithotomy; Micro-PCNL= Micro Percutaneous Nephrolithotomy; Ultra-mini-PCNL= Ultra-Mini Percutaneous Nephrolithotomy; RIRS= Retrograde Intrarenal Surgery; ECIRS- Endoscopic Combined Intrarenal Surgery; SFR= Stone-Free Rate; DTPA= Diethylenetriaminepentaacetic Acid

1. Abstract

1.1. Objectives: To assess the success of flexible ureterorenoscopy (f-URS) in patients with nephroureterolithiasis ≥ 15 mm and in patients with nephrolithiasis only.

1.2. Patients and Methods: Of 5,707 patients with upper urinary tract (UUT) stones who underwent ureterorenoscopy by one surgeon between April 2010 and April 2020, 112 consecutive renal units with UUT stones ≥ 15 mm who underwent f-URS in one center were selected for this study. They were divided into two groups: Group I: nephroureterolithiasis, and Group II: nephrolithiasis only. The primary endpoint was the stone-free rate (SFR).

This study was retrospective, with all the data recorded prospectively.

1.3. Results: The mean patient age was 49.9 years and 52.2 years in Groups I and II, respectively ($p > 0.05$). The mean stone sizes were 27.8 mm and 20 mm in Groups I and II, respectively ($p < 0.05$). The mean number of procedures per renal patient was 1.240 (62/50) and 1.242 (77/62) in Groups I and II, respectively ($p > 0.05$). The SFRs of the single session and the two-stage procedure were 76% (38/50) and 75.8% (47/62) and 100% (12/12) and 100% (15/15) in Groups I and II, respectively. There was no statistically significant difference regarding postoperative Clavien–Dindo complications.

1.4. Conclusions: Retrograde intrarenal surgery is a safe and effective method to surgically manage patients with concomitant large-burden renal and ureteral calculi. We suggest f-URS as the first-line treatment for these patients with stones equal to or larger than 15 mm. Further randomized trials are needed to confirm these findings.

2. Introduction

Nephrolithiasis is a common condition in Asia, with a rate of 1%-5% [1]. For decades, minimally invasive modalities have been used to treat urolithiasis. Examples of minimally invasive modalities include percutaneous nephrolithotomy (PCNL), mini-PCNL, micro-PCNL, ultra-mini-PCNL, and retrograde intrarenal surgery (RIRS), and supine PCNL [1-18]. Endoscopic combined intrarenal surgery (ECIRS) is another minimally invasive method. More than a decade ago, ECIRS is a new approach for performing PCNL in a modified supine position, approaching antero-retrogradely to the renal cavities and exploiting the full array of endourologic equipment [19, 20]. According to the EAU guidelines, PCNL or f-URS is recommended for lower pole stones larger than 15 mm [21]. Currently, f-URS has exceeded other modalities by 30% and is used as a first-line treatment modality for renal stones in many countries around the world [22-24]. Several reports in the literature have

discussed standard PCNL and its modifications, the prone position versus the supine position, and PCNL (all methods) versus RIRS [2-17]. To the best of our knowledge, there are no previous studies on the comparison between RIRS for large renal stones ≥ 15 mm with synchronous ureterolithiasis and RIRS for large renal-only stones ≥ 15 mm. From a pure probabilistic viewpoint, the simultaneous removal of stones from two different locations in a single procedure is more likely to be successful than in two independent procedures. Moreover, the cost of two independent procedures is more than double the cost of a single procedure of the same sort. Therefore, if the success rate of the joint procedure is equal to, or higher than, the success rate of each individual procedure, or if the complications rate of the joint procedure is equal to, or lower than, the complications rate of each individual procedure, then a joint procedure to remove stones from all locations is preferred compared to multiple removal procedures.

3. Patients and Methods

Of 5,707 patients with renal and/or ureteral stones who underwent ureterorenoscopy by one surgeon between April 2010 and April 2020, 651 renal units underwent surgery in one center. Of these, 112 renal units with upper tract stones ≥ 15 mm met our inclusion criteria.

The inclusion criteria were as follows:

1. Upper urinary tract stones ≥ 15 mm
2. The same flexible ureteroscope (flexible uretero-roscope FLEX- X2s [Karl Storz & Co. KG, Tuttlingen, Germany]) was used.
3. Use of the holmium: YAG laser energy (fibers 272 μ and 230 μ).
4. Use of the Laser generator sphinx jr. 30 watts [LISA Laser Products GmbH, Germany] or Mega Plus 15 Watt [Richard Wolf GmbH, Knittlingen, Germany].
5. A ureteral access sheath (Flexor ureteral access sheath 12/14F, 28, 35 or 45 cm; FUS- Cook Medical, Bloomington, IN, USA) was used.
6. All recorded data are available.
7. Adults aged 18 years and older.

The exclusion criteria were as follows:

1. Another flexible ureteroscope was used (not flexible uretero-roscope FLEX- X2s [Karl Storz & Co. KG, Tuttlingen, Germany]).
2. Comorbidities that interfered with the completion of the study, including severe systemic disease, congestive heart failure, pregnancy and severe chronic lung disease.
3. Patients with missing data.
4. No ureteral access sheath was used.

The primary endpoint was the stone-free rate (SFR). The SFR was defined as no remaining residual fragments. At the end of the oper-

ation, a triple test was performed in all calyces:

- A. Using a plain abdominal radiograph of the kidneys, ureters and bladder.
- B. Using the scope and the c-arm while injecting contrast intraoperatively during retrograde pyelography.
- C. Screening every calyx simultaneously using the endoscope and following the anatomy on the C-arm screen.

We evaluated 112 consecutive renal patients who underwent f-URS for large UUT stones ≥ 15 mm.

The renal patients were divided into two groups: Group I: nephro-ureterolithiasis ≥ 15 mm and Group II: nephrolithiasis (only) ≥ 15 mm.

In Group 1, we used the short ureteral access sheath (28 cm) in 19 patients with distal ureteral stones and inserted the scope through the ureteral orifice, inspected the ureter and treated the stones, and then passed it up using the guidewire to continue the procedure. This study was retrospective, with all the data (demographic data, stone characteristics, operative data, and postoperative data) recorded prospectively. Postoperative follow-up was scheduled one month after the procedure using a renal DTPA scan. Patients with residual stones were scheduled for a second RIRS.

For the analysis, we first compare the demographic characteristics and stone characteristics of the two main groups: Group I and Group II. The variables that were compared were sex composition of the patients, age, Hounsfield units, maximum (collective) stone diameter, lateralization, and the mean stone diameter in the upper-middle calyx and in the lower pole. We then compared the SFR in the first session, success in the second session, auxiliary procedures for the renal patients, ureteral stent placement, and complication rates.

We used t-tests to compare the means between the groups, assuming unequal independent distributions and similar distributions of the variables in the Kolmogorov–Smirnov test. Likewise, we report the “normalized difference” between the variables; see Asali (2019) and Asali et al. (2018) for discussion of these methods [25, 26]. We also studied the difference in the success rate, the auxiliary procedures, and the complication rates using a multivariate regression framework and considered the differences between the two groups regarding the background variables, including the demographic variables and the stone characteristics (size and location), to control for confounding variables.

4. Results

(Table 1) provides descriptive statistics of the main variables in this study. In particular, the table compares the means of the demographic and characteristic variables between the two groups. The third column of the table reports the difference in the means of the different variables, as well as the p value from the t-statistic testing the equality of these means; it also reports the p value from the

Kolmogorov–Smirnov test of equal distributions of the variables. As is clear from the table, the average of the variables, as well as their distributions, are similar for all the variables (gender, age, HU, upper calyx diameter, and lateralization). Understandably, the difference in the means and the distribution of the total stone diameter are highly statistically significant—obviously with larger figures for Group I.

The table also reports the “normalized difference” between the means of the variables. The normalized differences confirm the findings from the statistical mean and distribution comparisons, in that all the demographic and characteristic variables in the two groups are similar and comparable. In particular, the mean patient age was 49.9 years and 52.2 years in Groups I and II, respectively ($p>0.05$). The mean stone sizes were 27.8 mm and 20 mm in Groups I and II, respectively ($p<0.05$). The proportions of lower pole stones were 68% (34/50) and 54.8% (34/62) ($p>0.05$) in Groups I and II, respectively. The mean diameters of the lower pole stones were 8 mm and 10.5 mm in Groups I and II, respectively ($p>0.05$). The mean diameters of the upper and middle calyces were 9.8 mm and 10.4 mm in Groups I and II, respectively ($p>0.05$). Ureteral stone characteristics are shown in (Table 2). The table shows higher means and variances at the extreme points of the ureter. The univariate analysis of the main variables of interest showed that the term “first success” refers to the relatively equal SFRs and equal complication rates in the first session for Groups I and II (Table 3). The Clavien–Dindo classification was used to report complications [27]. There was no avulsion of the ureters and no need for conversion to open surgery in any patient.

Complication grade I is defined as “mild” according to the Clavien–Dindo classification and mostly refers to complaints about pain and dysuria. Grade III complications occurred in two patients, both of whom had ureteral stricture and needed treatment with endoscopic laser ureterotomy. There was no statistically significant difference in postoperative Clavien I complications between Group I and Group II ($p>0.05$). Likewise, there was only one case of ureteral stricture (Clavien III) in each group, and the difference was statistically insignificant ($p>0.05$). The mean number of procedures per renal patient was 1.240 (62/50) and 1.242 (77/62) in Groups I and II, respectively ($p>0.05$). The SFR for patients who underwent a single session was 76% (38/50) and 75.8% (47/62) in Groups I and II, respectively ($p>0.05$). The SFR for patients who underwent the two-stage procedure was 100% (12/12) and 100% (15/15) in Groups I and II, respectively. Ureteral double-J stents were inserted in 74% (37) and 83.9% (52) in Groups I and II, respectively ($p>0.05$). In the remaining patients, a ureteral cath-

eter was inserted for 14–24 hours. Because we are dealing with large-burden stones and prolonged procedures, we inserted JJ stents in most of the patients, as ureteral edema in these patients require time to resolve. JJ stents were inserted preoperatively in 8 patients (8/50) in Group I and in 9 patients (9/62) in group II. The length of hospital stay was one day in both groups.

In a multivariate analysis, we can more accurately identify the true net difference in the variables of interest (success rate and complication rates) to control for different demographic variables and stone characteristics. The success rate (SFR in the first session) are provided in (Table 4). Column 1 of the table shows the unconditional difference between the two groups—this is equal to the earlier figures shown in Table 3 (first row, third column). There is no statistically significant difference, implying that the success rate is not affected by the mode of surgery, renal stone removal or the simultaneous removal of renal and ureteral stones. In Column 2, we control for the demographic variables of the patients, mainly patient age (and squared age, to allow for nonlinearities in the effect) and sex. The coefficient of the ureter is still not different from zero at any conventional statistical level, implying equal success rates for the two groups. Once we control for the stone characteristics in Column 3, however, we see that the coefficient of the ureter becomes significantly larger and statistically significant at all conventional levels. It turns out that, once we control for the demographic and characteristic differences, surgery to simultaneously remove all stones has a higher success rate in Group I. Incidentally, it is also clear from the table that age and sex have no effect on the success rate and that the success rate is negatively affected by the total size (diameter) of the removed stones. In (Table 5), we report a similar analysis for the complication rates, including mild and severe complications, between the groups. Notice first that the unconditional differences, mild complications are measured in Column 1 and severe complications are measured in Column 3, are equal (in absolute value) to the reported figures in the last two rows of (Table 3). It is clear that there was no difference in the rate of severe complications between the two groups, even after controlling for demographic and characteristic variables, as shown in Column 4. However, it appears that joint surgery (Group I) is less likely to result in mild complications, as reported by the negative coefficient of -0.071 in Column 2. The effect is significant at the 5% level (Table 5). Once again, demographic variables seem to play no role in the complication rates—although age seems to have a small, positive effect on mild complications (0.01 from Column 2) but that effect is only marginally statistically significant (at the 10% level).

Table 1: Patient demographics and stone characteristics.

	Group I (A Combination of Renal and Ureteral Stones)	Group II (Renal Stones only)	Difference (P value) [KS P value]	Normalized difference
Patients	45	56		
Sex M/F	32/13	40/16		
Renal Patients	50	62		
Male	0.74	0.69	0.046	0.072
			(-0.59)	
			[1.0]	
Age (years)	49.9	52.2	2.322	0.116
			(-0.39)	
			[0.21]	
Hounsfield unit	890.4	880.4	10.045	0.031
			(-0.82)	
			[0.81]	
Previous surgery a	0.04	0.032	0.008	0.029
			-0.83	
			[1.0]	
Mean stone Max. Diameter (mm)	27.8	20	7.788	0.495
			(-0.001)	
			[0.022]	
Mean Upper and Mid. Calyx Max. Diameter (mm)	9.8	10.4	0.613	0.083
{observations}	{28}	{23}	(-0.679)	
			[0.364]	
Mean Lower Pole Diameter (mm)	8	10.5	2.559	0.336
{observations}	{34}	{34}	(-0.055)	
			[0.029]	
Lateralization R/L	26/24	31/31	0.02	0.028
			-0.84	
			[1.0]	

Notes: The differences are reported in means (between Groups I and II), with a p value for the null hypothesis of equal means, and the “normalized differences,” whose values, if below 0.25, are deemed negligible. See Asali et al. (2018) for details on its calculation and use. Additionally, reported are the Kolmogorov–Smirnov (KS) p values of the test of equal distributions between the groups. See Asali (2019) for details on this measure. (a) “Previous surgery” refers to 2 cases of previous surgeries in each group (pyeloplasty and PCNL in Group I, and pyeloplasty and multiple ureteroscopy in group II).

Table 2: Group I Ureteral Stone Characteristics.

Group I (Combination of Renal and Ureteral Stones)	Upper Ureter	Mid. Ureter	Lower Ureter
No.	24	12	19
Mean Stone Diameter (mm)	11.5	9.3	12.1
Standard deviation	5.13	3.93	5.75
Range	[5, 22]	[3, 18]	[7, 30]

Table 3. Postoperative Results.

	Group I (Combination of Renal and Ureteral Stones)	Group II (Renal Stones only)	Difference (P value) [KS P value]	Normalized difference
Stone Free Rate in first session	38/50 (76.0%)	47/62 (75.8%)	0.20%	0.003
			-0.981	
			[1.00]	
Second Session	12	15		
Stone Free Rate in second session	12/12 (100%)	15/15 (100%)	0	0
			-1	
			[1]	
Auxiliary Procedures for Renal Patients	62/50 (1.240)	77/62 (1.242)	0.002	0.003
			-0.981	
			[1.00]	
Ureteral Stent Placement	37 (74.0%)	52 (83.9%)	9.90%	0.171
			-0.211	
			[0.950]	
Complication Grade III (Clavien-Dindo classification)	2.0% (1/50)	1.6% (1/62)	0.40%	0.02
			-0.881	
			[1.0]	
Complication Grade I	4.0% (2/50)	6.5% (4/62)	2.50%	0.077
			-0.562	
			[1.0]	

Notes: See notes of Table 1 for details.

Table 4: The effect of simultaneous removal of ureteral and renal stones on the probability of stone-free rates in the first session.

	-1	-2	-3
Ureter	0.002	0.009	0.227***
	-0.082	-0.085	-0.064
Age		0.002	0.013
		-0.018	-0.014
Age2 (x1000)		0.001	-0.072
		-0.173	-0.13
Male		-0.039	-0.109
		-0.092	-0.07
Total diameter			-0.027***
			-0.003
HU (x1000)			0.006
			-0.165
Right kidney			0.051
			-0.065
Observations	112	112	112
R-squared	0	0.007	0.424

Notes: “Ureter” takes on the value 1 if the patient had and underwent a procedure to simultaneously remove both ureteral and renal stones, and 0 if the patient only had renal stones. Robust standard errors are in parentheses.

*** p<0.01

Table 5: The effect of simultaneous ureteral and renal stone removal on the probability of mild and severe complications.

	M i l d complication		S e v e r e complication	
	-1	-2	-3	-4
Ureter	-0.025	-0.071**	0.004	0.015
	-0.042	-0.032	-0.026	-0.028
Age		0.010*		0.005
		-0.005		-0.004
Age2 (x1000)		-0.092		-0.045
		-0.055		-0.035
Male		0.029		0
		-0.049		-0.032
Total diameter		0.006*		-0.001
		-0.003		-0.001
HU (x1000)		0.093		0.045
		-0.09		-0.036
Right kidney		0.048		0.037
		-0.043		-0.027
Observations	112	112	112	112
R-squared	0.003	0.149	0	0.105

Notes: “Ureter” takes on the value 1 if the patient had both ureteral and renal stones and underwent a procedure to simultaneously remove the stones, and 0 if the patient only had renal stones. A mild complication is defined as LEVEL I. SEVERE... Robust standard errors in parentheses.

** p<0.05, * p<0.1

5. Discussion

RIRS is a safe and valuable alternative option to manage large renal stones. It is a well-established procedure that is being continuously improved by advances in technique and technology. It has gained worldwide popularity due to its minimal invasiveness and satisfactory outcomes [13]. Bryniarski et al., in their randomized study of renal stones larger than 2 cm, showed that PCNL was more effective (94%) when compared with RIRS (75%), but it is worth emphasizing that they used a semirigid ureteroscope, not a flexible ureteroscope, which would have been more successful [15].

Advances in flexible ureteroscope design and accessory instrumentation, as well as the introduction of new laser generators, have allowed more challenging cases to be treated ureteroscopically. Several articles discussed RIRS and compared it with other minimally invasive surgeries. Zeng et al. showed that supermini PCNL was more effective than RIRS in treating 1-2 cm lower-pole renal stones in terms of a better SFR and lower auxiliary procedure rate but caused more postoperative pain [3]. Moreover, Kang et al. concluded, in a meta-analysis, that RIRS can be a safe and effective procedure for selected patients with large renal stones, but the SFR was higher in patients who underwent PCNL [9], despite acknowledging the known differences in complications between PCNL and RIRS.

RIRS was also compared with PCNL in pediatric patients with upper tract stones. There was no significant difference in operation time, and for stones smaller than 20 mm, there was no significant

difference in the SFR between patients who underwent PCNL or RIRS, although RIRS might have been associated with shorter hospital stays [10]. Gao XS et al., in their systematic review of mini-PCNL, ultra-mini-PCNL, micro-PCNL and RIRS, found that mini-PCNL for lower pole stones resulted in a significantly higher SFR than RIRS, although RIRS was associated with a shorter hospital stay and less hemoglobin drop [11].

Kılıç Ö et al. concluded that RIRS can be used as a primary treatment in patients with renal stones smaller than 2 cm, with prior unsuccessful shock wave lithotripsy, infundibular stenosis, re-noureteral malformation, skeletal-muscular deformity, bleeding diathesis and obesity [12]. In contrast, Cepeda M et al. concluded that micro-PCNL was an effective and safe procedure for the treatment of renal lithiasis smaller than 2 cm, thus suggesting that it is a good alternative to retrograde intrarenal surgery for this stone size. However, it is worth noting that the number of patients in their study was too small [6]. Breda et al., in their review, although not supported by strong evidence, observed that, in selected patients with renal stones larger than 2 cm, RIRS resulted in acceptable efficacy with low morbidity [28].

Recently, Ho et al., in their review, highlighted the expanding role of URS in managing more complex stones and achieving good patient outcomes [16]. Barone et al. conducted a systematic review and a meta-analysis, in which they concluded that RIRS is competing with PCNL as the preferred treatment for renal stones larger than 2 cm but RIRS is becoming a safe and effective alternative with a comparable stone-free rate, a lower complication rate, and a

shorter duration of hospitalization. However, they suggest that we collaborate with the patient in the decision-making process due to the possibility of requiring multiple RIRS sessions to completely clear larger stone burdens [29]. In our series, we also showed that using this modality is safe in patients with synchronous nephroureterolithiasis. In all our patients, we used a holmium laser with fibers (230 μ and 272 μ) and the same ureteroscope (Karl-Storz flex-x2s). The access sheaths were 12/14 cm, 28 cm, 35 cm, or 45 cm from the same manufacturer, and all the patients were treated by the same surgeon.

We showed that in a single session, RIRS was successful in 76% of the patients with nephroureterolithiasis in the first group and in 75.8% of the patients with renal stones only in the second group, and we showed that the difference was not significant ($p>0.05$). A second session was needed for 12 renal patients (24%) and for 15 renal patients (25.8%) in Groups I and II, respectively. There was never a need for a third session in either group. The mean number of procedures per renal patient was similar in both groups (1.24). We achieved good results, although there were more lower pole stones in Group I (68%) than in Group II (54.8%) ($p>0.05$). Kandemir et al. compared micro-PCNL and RIRS for lower pole kidney stones with diameters up to 15 mm in their prospective randomized study. They concluded that micro-PCNL and RIRS were safe and effective alternatives and had similar stone clearance and complication rates. However, micro-PCNL was a time-consuming procedure and resulted in prolonged hospital stays. Moreover, the renal tubular damage caused by both of these methods should be evaluated [4]. Similarly, Jiang et al., in their review comparing mini-PCNL and RIRS, showed a significantly higher SFR in patients with renal calculi who underwent mini-PCNL, and the procedure resulted in higher postoperative complications and longer hospital stays [7]. Demirbas et al. concluded that ultra-mini-PCNL and RIRS procedures were effective and safe methods for the treatment of renal stones diameters ranging from 10 mm to 25 mm. However, ultra-mini-PCNL was more effective than RIRS in treating lower pole stones [5]. Scoffone et al. introduced a new standard for percutaneous nephrolithotomy called ECIRS, which allowed PCNL and RIRS to be simultaneously performed, and was associated with a high SFR and anesthesiological advantages [19]. In our study, we evaluated the use of f-URS in stones larger than 15 mm, either in the kidney only or in both the kidney and the ureter. Our main findings show that the success rate of the joint procedure is equal to or higher than that of the individual procedure. Likewise, albeit with weaker evidence, we find that the complication rate (based on the Clavien–Dindo classification) of the joint procedure is equal to or less than that of the individual procedure. Hence, our main finding suggests that, for patients with nephroureterolithiasis, a joint procedure is strictly preferred, compared to two (or more) procedures, to separately remove each of the stones.

6. Conclusions

Retrograde intrarenal surgery lithotripsy is a safe and effective method of surgically managing patients with large renal stones only and for patients with both renal and ureteral calculi. We suggest f-URS as the first-choice treatment for these patients with stones larger than 15 mm. A higher SFR in the first session suggests that a single procedure is preferred to surgically manage patients with renal and ureteral calculi. Further randomized trials are needed to confirm these findings.

7. Author Disclosure Statement

No competing financial interests exist.

8. Funding Information

No funding was received for this study.

9. Ethical Approval

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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