The Fate of Residual Fragments After Retrograde Intrarenal Surgery in Long-Term Follow-up

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Purpose: We aimed to describe the natural history of stone fragments ≤ 7 mm that remained after retrograde intrarenal surgery (RIRS) in long-term follow-up.

Materials and Methods: We retrospectively reviewed 142 medical records of patients who had residual fragments (RFs) ≤ 7 mm after RIRS. Patients were divided into 2 groups according to the size of RFs as ≤ 4 mm (group 1) and 5 – 7 mm (group 2). Patients' demographic data, stone characteristics, perioperative data and complications were recorded. Re-growth of RFs, spontaneous passage, renal colic, infection and re-operation rates were our main variables.

Result: A total of 142 patients (86 in group 1 / 56 in group 2) were followed for mean 54.45 ± 14.24 and 56.22 ± 10.28 months. Mean size of RFs was 2.85 ± 1.22 mm in group 1 and 6.81 ≤ 2.21 mm in group 2. Mean number of RFs were 1.1 ± 0.2 in group 1 and 2.4 ± 1.6 in group 2 (P = .035). Spontaneous passage rate of RFs were 30.23% and 17.85% in group 1 and 2, respectively (P = .032). No difference was observed in the re-growth rate of RFs between the two groups (P = .094). Although no difference was observed in re-growth of RFs between the groups, patients in group 2 were more likely to experience stone-related events such as renal colic and re-intervention rate (P = .034, P = .029; respectively).

Conclusion: Our results demonstrate that RFs > 4 mm take higher risk in terms of stone-related events and should be followed up more closely.

Keywords: natural history; renal stone; residual fragments; RIRS; spontaneous passage

INTRODUCTION

Retrograde intrarenal surgery (RIRS) have become a widely used modality with low complication and high success in the treatment of kidney stones in recent years.[(1)] Compared to extracorporal shockwave lithotripsy (ESWL), RIRS has higher success rate with less pain in the treatment of renal stones ≤ 2 cm.[(2)] Because of its low complication rate compared to the percutaneous nephrolithotomy (PCNL), indications of RIRS for the treatment of renal stones have expanded for even stones larger than 2 cm.[(3-5)]. In the current literature, stone free rate (SFR) of RIRS procedures were varying between 73.6% and 94.1%; on the other hand, RF rates after RIRS procedures range from 5.9% to 26.4%.[(6)]

Residual stone fragment (RF) is defined as the remaining fragments after any surgical or non-surgical intervention. RF which is asymptomatic, non-infectious, non-obstructive and ≤ 4 mm in size is accepted as clinically insignificant residual fragments (CIRF).[(7,8)] Stone growth and recurrence, urinary tract infection, ureteric obstruction are the potential complications of these RFs.[(9,10)]

With the advancement of modern technologies, minimally invasive methods such as ESWL, PCNL, RIRS and laparoscopic procedures are all used more effectively for the treatment of renal stones. However, RFs after these minimally invasive procedures are still a problem during the follow-up. In the literature, complication rates due to the RFs are varying between 18.1% and 59% according to the performed procedures.[(10,11)] In a prospective study published by Streem et al., 18.1% of the fragments were experienced re-growth, 41.9% of the residual fragments were not changed at all and 36% spontaneous passage occurred within the first year after the ESWL procedure.[(11)] Altunrende et al. found that 22% of the patients who underwent PCNL operation had residual fragments in a 3-year follow-up, 21.1% of these RFs showed an increase in size, 71,1% of RFs stayed stable or decreased in size and 7.9% patients had spontaneous passage.[(12)] In the study of Ozgor et al., 34% re-growth of CIRF was observed after RIRS operation in 30-month follow-up period.[(13)]

In the literature, there are several studies about the natural course of CIRF after ESWL, URS, and PCNL; however, there are not enough clinical trials investigating RF after RIRS.

In this study, we aimed to describe the natural history of stone fragments smaller than 7 mm that remained after RIRS procedures in long-term follow-up.

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Received August 2017& Accepted April 2018

Table 1. Patient demographics, preoperative and perioperative findings.

	≤ 4 mm	5-7 mm	
Mean age (year)	45.4 ± 16.6	39.2 ± 11.4	*P* = .247
Gender (male/female)	58/28	24/32	*P* = .437
Stone opacity (opaque/non-opaque)	72/14	46/10	*P* = .894
Stone size before RIRS (mm)	16.36 ±7.1	22.08 ± 7.5	*P* = .028
Stone number	1.14 ± 0.4	1.86 ± 1.8	*P* = .046
Hydronephrosis			*P* = .595
None	32	20	
Grade 1	26	18	
Grade 2	14	12	
Grade 3	14	6	
Operation time (min)	41.17 ± 14.23	56.21 ± 20.17	*P* = .044
Fluoroscopy time (min)	3.02 ± 2.34	3.22 ± 4.07	*P* = .760
Hospitalization time (day)	1.68 ± 2.95	1.81 ± 3.04	*P* = .685
Mean follow-up (month)	54.45 ± 14.24	56.22 ± 10.28	*P* =. 087

Data is presented as mean ± SD or number (percent)

MATERIALS AND METHODS

We retrospectively reviewed the medical records of 1048 patients who underwent RIRS at Istanbul Medeniyet University Goztepe Training and Research Hospital from May 2008 to April 2016. Of them, 142 patients who had ≤ 7 mm RF after RIRS procedures and at least 12 months follow-up were included into the study. The patients who have asymptomatic residual fragments ≤ 7 mm after the RIRS operation at 3 months postoperatively were included for the study. The patients who had residual fragments > 7 mm accepted as a treatment failure and excluded from the study. RFs were detected with computed tomography (CT). The size of multiple residual fragments apart from each other was measured with sum of the long axis of each RF. The patients with unsuccessful RIRS procedure and who required a repeated stone removal procedure within three months postoperatively were excluded from the study (Figure 1). Gender, age, history of ESWL or stone surgery, and comorbidities were recorded as patients' characteristics. Preoperative parameters such as stone diameter, numbers, burden, laterality, location and opacity, a presence of renal anomalies, grade of hydronephrosis were evaluated with CT. Operation time, hospitalization time, fluoroscopy time, postoperative complications, and number, burden, a location of RFs were also recorded. Patients were divided into 2 groups according to the size of RF as ≤ 4 mm and 5-7 mm. Re-growth of RFs, spontaneous passage, renal colic, infection and re-operation rates were main outcome variables.

Serum biochemistry, complete blood count, urine analysis and urine culture were performed for all patients prior to surgery. All patients had sterile urine culture prior to surgery. Urinary tract infection was treated according to sensitivity results of the urine culture. The procedures were performed in lithotomy position under general anesthesia. We performed semi rigid ureteroscopy firstly to create the ureteral dilation before placing ureteral access sheath (UAS). 7.5 Fr flexible ureteroscope (FLEX-X2, Tuttlingen, Germany) was advanced through the 9.5 -11 fr UAS. The f - URS was passed over the guidewire in the case of unsuccessful placement of UAS. In all cases, 200 or 273 µm laser fiber was used for stone fragmentation. Stones were fragmented into pieces as small as possible and were left spontaneous passage. At the end of the procedure, a double-J (4.7 fr) stent was inserted in all cases. Double-J stents were removed 2 - 4 weeks after the operation.

Table 2. RF characteristics and postoperative follow-up data.

	≤ 4 mm	5-7mm	
Mean RF burden (mm)	2.85 ± 1.22	6.81 ± 2.21	*P* = .004
Mean RF number	1.1 ± 0.2	2.4 ± 1.6	*P* = .035
Spontaneous passage	26/86 (30.23%)	10/56 (17.85)	*P* = .032
Lower pole	6/36 (16.6%)	2/18 (11.1%)	
Middle/upper pole	10/32 (31.25%)	2/22 (9.09%)	
Multiple calix	4/8 (50%)	2/10 (20%)	
Renal pelvis	6/10 (60%)	4/6 (66.6%)	
Re-growth	18 (20.93%)	12 (21.42%)	*P* = .094
Lower pole	7	5	
Middle/upper pole	4	3	
Multiple calix	7	4	
Renal pelvis	-	-	
Renal Colic	24 (27.90%)	8 (14.28%)	*P* = .034
Urinary infection	6 (6.97%)	4 (7.14%)	*P* = .083
Re-operation	16 (18.60%)	18 (32.14%)	*P* = .029
ESWL	8	8	
PCNL	0	2	
f-URS	4	4	
URS	2	4	
DJ stent insertion and delayed URS because of urosepsis	2	0	

Data is presented as mean ± SD or number (percent)

Table 3. Stone analysis results.

Stone Analysis Results	≤ 4 mm	5-7 mm
Unknown	26 (30.23%)	16 (28.57%)
Ca oxalate/phosphate	28 (32.55%)	18 (32.14%)
Uric acid	8 (9.30%)	4 (7.14%)
Cystine	6 (6.97%)	8 (14.28%)
Struvite	6 (6.97)	2 (3.57%)
Mixed	12 (13.95%)	8 (14.28%)

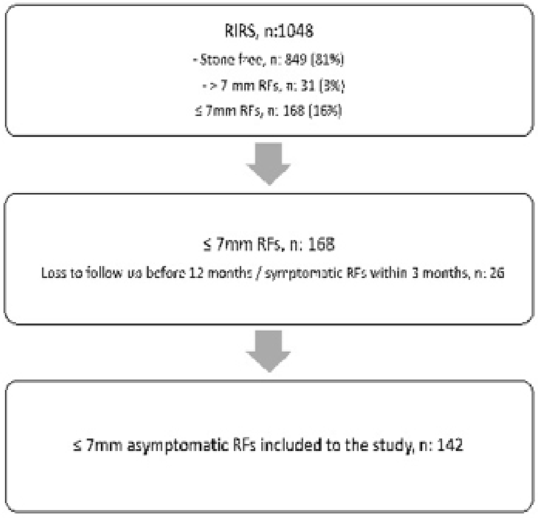

Figure 1. Trial flow diagram

We performed CT in the 3rd months of follow-up. Patients were accepted as stone-free when there was no residual fragments on CT on follow-up. The frequency of visits and imaging methods (CT / ultrasonography or kidney-ureter-bladder x-ray) to be used in each visit was determined according to RF burden, localization, and the presence of obstruction and symptoms of patients during the follow-up. If the patient had RF and was asymptomatic, CT scan performed yearly. If available, stone analyses were done and all patients underwent a metabolic evaluation at 1 month postoperatively. Dietary suggestions were made for all patients and if necessary patients treated with appropriate medical treatment according to metabolic evaluation or stone analysis.

Statistical analyses were performed via SPSS software, version 21.0 (IBM, Armonk, NY). The data were expressed as the mean ± standard deviation or frequency. The Kolmogorov-Smirnov test was used to test the normal distribution of the variables. The categorical variables were compared with the Chi squared test, and the continuous variables were compared with an unpaired t test or the Mann–Whitney U test. A p value ≤ 0.05 was considered to be significant.

RESULTS

In our study RF rate was detected %13.54 (142 / 1048). A total of 142 patients (86 in group 1 / 56 in group 2) were followed for a mean of 54.45 ± 14.24 and 56.22 ± 10.28 months respectively. Mean stone size and number before the operation were 16.36 ± 7.1 mm and 1.14 ± 0.4 in group 1, 22.08 ± 7.5 mm and 1.86 ± 1.8 in group 2, respectively (P = .028 / P = .046). The pre-operative and operative characteristics of patients were summarized in **Table 1**.

Mean size was 2.85 ± 1.22 mm in group 1 and 6.81± 2.21 mm in group 2. Mean number of RFs was 1.1 ± 0.2 in group 1 and 2.4 ± 1.6 in group 2 (p = .035). Spontaneous passage rate of RFs were 30.23% and 17.85% in group 1 and 2, respectively (P = .032). No differences were observed in the re-growth rate of RFs between the two groups (P = .094). Although no difference was observed in re-growth rate between the two groups, patients in group 2 were more likely to experience stone related events such as renal colic and re-intervention (P = .034, P = 0.029; respectively). A total of 16 patients in group 1 and 18 patients in group 2 needed additional procedures (**Table 2**).

The stone analysis was available for 60 and 40 patients in group 1 and 2, respectively. The stone analysis results are shown in **Table 3**.

DISCUSSION

RFs that are asymptomatic, non-infectious, non-obstructive and in ≤ 4 mm size is generally accepted as CIRF.[7] This term is not accepted as an innocent definition by some authors because almost 59% of these fragments require re-admission to the hospital.[10] However, there are not enough studies evaluating the natural course of RFs after endourological procedures. Herein we both evaluated the natural course of RFs after the RIRS procedures in long-term follow-up and also compared RFs according to the size in terms of spontaneous passage, stone-related events and re- intervention rates.

There are several studies describing the natural course of RFs after PCNL and ESWL. High stone burdens, multiple access requirements, stone location in different calyces, restriction of visualization due to hemorrhage during the operation were some of the reasons of the RFs after PCNL. Fragmentation technique in PCNL (ultrasonic or pneumatic) was another reason of the high RFs rates according to some studies.[14,15] But, conversely to these studies in a prospective research Radfar MH et al reported that there were no statistically significant differences in RFs rates between pneumatic and ultrasonic lithotripsy.[16]

In a study conducted by Ganpule et al., 7.57% RF was observed and, 65.47% of these RFs spontaneously passaged after 3 months. They found that RFs smaller than 25 mm^2 and the renal pelvis localization had the highest chance of spontaneous passage.[6] Raman et al. reported 8% RFs rate in the patients who underwent PCNL procedure.[17] 42.8% of patients with residual fragments were found to have stone-related symptoms during the follow-up and 26% of these patients required secondary intervention. The rate of symptomatic attack and secondary intervention due to residual fragment was found to be higher in stones localized in renal pelvis and ureter and in patients with RF greater than 2 mm.[17]

In our study, similarly to the literature regarding natural course of RFs after PCNL, spontaneous passage rate was higher in patients with RFs smaller than 4 mm and RFs located in the renal pelvis. Moreover, the re-intervention rate was higher in RFs larger than 4 mm.

The rate of residual fragment detection after ESWL procedures is still quite high. It is proved that the stones larger than 20 mm, increased stone number, cystine-brushite-calcium oxalate monohydrate stone types were the negative predictive factors that affect the RF

rates after ESWL procedures.[18,19] In the literature, stone events due to RF after ESWL procedures have been reported between 18.1% and 59%.[10,11] In a prospective study published by Streem et al., 160 patients with RFs were followed up for 89 months and re-growth of RFs was detected in 18.1% of these patients, 41.9% of the RFs were unchanged and spontaneous passages was observed in 36%.[11] In contrary to the reported natural course of RFs after ESWL, re-intervention rates in our study were lower in even RFs ≤ 4 mm group than the reported re-intervention rates after ESWL. We thought that higher spontaneous passage rates after RIRS compared to ESWL may be due to passive ureteral dilatation effect of Double-J stent insertion after RIRS.
Since RIRS is a new treatment modality, there are not enough studies in the literature regarding the fate of RFs after the RIRS procedures. Ozgor et al. reported a 34% re-growth rate in 44 patients in 30-month of follow-up period.[13] Rebuck et al. showed that 19.6% of the patients with RFs had a stone-related attack in 19.9 months of follow-up period.[20] In a study conducted by Chew et al. with the participation of 6 centers, the data of 232 patients with RF after RIRS were retrospectively reviewed.[21] Fifty six percent of these patients did not need additional intervention and remained asymptomatic, 15% had experienced a stone-related attack without a need of additional intervention and 29% had undergone an additional intervention.
Moreover, patients with RF larger than 4 mm were found to have a higher risk of recurrence and stone related events. Similar to these studies, in our study, we detected a positive correlation between the RF size and the re-intervention rate. However, there was no statistically significant difference in growth rate between the two comparison groups of RF size. This may be explained by the follow-up with appropriate medical treatment.
Pelvicalyceal anatomy and the calyceal localization of the RFs are well-known factors that may affect the spontaneous passage rate. Several studies have shown lower clearance rates in RFs located in the lower calyces than in the middle and/or upper calyces.[22,23] In contrast, Rebuck et al. reported that there was no difference in the spontaneous passage rates between the RFs located in lower and non-lower pole.[20] In our study, we observed the highest spontaneous passage rates in renal pelvis than the other calyceal localizations.
Different fragmentation techniques such as dusting and drilling have been used to treat renal stones ureteroscopically. Chew et al. found that patients treated with dusting techniques had a shorter time to a subsequent stone event than patients treated with drilling and basketing technique.[21] In our study group, stones were fragmented into pieces as small as possible and were left spontaneous passage. The superiority of a fragmentation technique over the other technique has not been proven yet in terms of the natural course of RFs.[24] Further studies are needed to compare the fragmentation techniques to determine the effect of fragmentation technique over the natural course of RFs.
Our study has some limitations. The main limitation of the study is its retrospective nature, which may result in differences in follow-up protocol such as frequency of visits and used imaging methods. In addition, despite the same surgical and fragmentation techniques were used in all cases, different surgeons were involved in the procedures. Lastly in our study all patients had received dietary instructions and some of them specific medical treatment. This might affect the re-growth rate and the absence of difference between the two groups regarding growth rate might have been the result of the specific medical treatment.
Despite these limitations, the present study is one of the largest series in the English literature and has the longest follow-up period, which evaluates the natural course of RFs.

CONCLUSIONS

Our results demonstrate that vast majority of RFs ≤ 4mm passed spontaneously or remained unchanged. However spontaneous passage rates of RFs in 5 - 7 mm in size were lower and re-intervention rates were higher than RFs ≤ 4 mm in size. Moreover, there were no statistically significant differences in re-growth rates and urinary tract infections between the RFs ≤ 4 mm and 5 - 7 mm. Taken together, our results suggest that RFs larger than 4 mm take higher risk in terms of stone-related events and should be followed up more closely.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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