

# Prognostic factors for the safety and efficacy of retrograde laser lithotripsy: Data from a contemporary series of 155 consecutive patients with single and multiple lithiasis of the urinary tract

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**Abstract.** Treatment of large and multiple stones located in the ureter and/or the kidney may be challenging. The aim of the current study was to evaluate the results and complications of retrograde endoscopic lithotripsy for stones located in the urinary tract and to determine prognostic factors for treatment outcome. From April 2017 to March 2020, eligible patients for the active treatment of ureterolithiasis with or without concomitant nephrolithiasis <20 mm were enrolled in the study. The prognostic factors for the stone free rate (SFR) after the 1st and subsequent sessions and overall complications were assessed. Patients were divided into single or multiple lithiasis groups (groups A and B respectively). A comparison between these two groups was then conducted. Overall, 237 stones were detected in 155 patients, representing a mean burden of 1.53 stone per patient. The mean total stone size was 14.7 mm, the initial SFR was 80% and the final SFR (after a mean of 1.23 session per patient) was 94.2%. The rate of complications was 26.4%. Multivariate analysis revealed that preoperative stenting and total stone size were independent

prognostic factors of initial SFR, while no independent factors were determined for final SFR. Age, total size and stones in the lower calyx were independent factors for complications. In group A and B, 114 and 41 cases with solitary and multiple stones were included, respectively. Excluding operation time ( $P=0.002$ ), no significant differences were recorded in terms of initial ( $P=0.255$ ) and final SFR ( $P=0.056$ ), hospital stay ( $P=0.308$ ), mean number of treatments ( $P=0.757$ ) and the rate of complications ( $P=0.218$ ) between the two groups. In conclusion, retrograde endoscopic management of multiple lithiasis has a favorable outcome irrespective of stone location. Older patients with higher burdens and stones in the lower calyx should be treated with caution.

## Introduction

Ureteroscopically guided laser lithotripsy (URL) is the treatment of choice for patients with ureterolithiasis (1,2). For large intrarenal stones percutaneous nephrolithotripsy (PCNL) is the mainstay of therapy in terms of stone free rates but at a cost of increased invasiveness (3). Smaller stones in the kidney can also be treated with ESWL or retrograde intrarenal surgery (RIRS) (3,4). There is an increasing body of evidence that for intrarenal stones  $\leq 20$  mm flexible retrograde lithotripsy may yield results comparable with those of PCNL but with reduced risk of complications (5-7). Furthermore, for medium and small sized stones located in the kidney, the superiority of PCNL over RIRS in terms of stone removal and the rate of complications is in contention (5).

Some patients harbor multiple stones in the same collecting system and the ureteroscopic access to the proximal stone may be impeded by the distal one. Treatment of large and multiple stones located in the ureter and/or the kidney may be therefore a challenging procedure. Apart from equipment availability, several other factors play important roles in the success of treatment, such as the location, the number and the size of stones (2). Evidence regarding the optimal treatment of multiple ipsilateral lithiasis is limited and EAU and AUA Guidelines provide no clear recommendations (3,4). However, for multiple ureterolithiasis, lithotripsy of as many

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**Abbreviations:** SFR, stone free rate; SFR1, stone free rate after the first session; SFRf, stone free rate after any subsequent session(s) after the first; URL, ureteroscopically guided laser lithotripsy; ESWL, extracorporeal shock wave lithotripsy; RIRS, retrograde intrarenal surgery; PCNL, percutaneous nephrolithotripsy; EAU, European Association of Urology; AUA, American Urologic Association; UTI, urinary tract infection; HU, hounsfield units; SR, semirigid; F, flexible; SD, standard deviation; IQR, interquartile range; djs, double j stent

**Key words:** ureterolithiasis, nephrolithiasis, multiple stones, lithotripsy, stone free

stones as possible is a reasonable treatment. For stones located simultaneously in the ureter and the kidney, fragmentation of the ureteral counterpart is initially performed and when the patency of ureter has been achieved removal of renal stones is attempted in a separate session of PCNL or ESWL.

Considering the improvements in the technology of flexible scopes, we investigated whether multiple ureterolithotripsy or ureterolithotripsy plus RIRS in a single session might have the potential to safely and effectively treat patients. To address this issue, the results of multiple lithotripsy are compared to the standard of care (single ureteral lithotripsy).

## Materials and methods

**Study population.** From April 2017 to March 2020, patients eligible for active treatment for ureterolithiasis or concomitant lithiasis of the ureter and the kidney were enrolled in the study and prospectively evaluated. Data regarding sex, age, history of urinary tract infection (UTI), laterality, number, size and location of stones, preoperative stenting, duration of operation, stone hardness (expressed in Hounsfield units-HU), use of semirigid (SR) and/or flexible (F) instruments, use of basket and access sheath were recorded and analyzed. End points were stone free rate (SFR) after a single and multiple treatments [SFR1 and SFR final (SFRf) respectively] and the rate of complications. The stone size was the maximum length of a solitary stone in CT scan or the sum of the maximum lengths in multiple lithiasis. The stone surface or the volume after 3D reconstruction might be more representative of the stone burden. However, the maximum length or the sum of maximum lengths have also been used in the literature to describe the stone burden (6,8-10). In the cases with multiple stones the HU was the mean value of the HU of each one. The operation time was calculated from the time the patient received anesthesia till the removal of the scope. Complications were graded according to the Clavien system (11). Analysis of stone composition was performed only in younger stone formers and in recurrent disease; hence stone composition was not formally included in the analysis.

**Treatment methods.** Criteria for exclusion were the presence of renal stones only, the renal stones greater than 20 mm, uncontrolled coagulopathy, pregnancy, staghorn calculi and active urinary tract infection. Previous treatment for lithiasis was not a criterion for exclusion. Prior to the operation all of the participants were informed about all the treatment options for single and multiple lithiasis. Detailed information was provided about results and complications of URL and RIRS, and patients signed the relevant informed consent. The methods of treatment meet the criteria of Helsinki declaration for human rights and the study was approved by the General Hospital of Volos' ethics committee (protocol number 3718/17-3-2017). Those who consented on the treatment had also the option to be included in the study. Single or multiple retrograde ureterolithotripsy was initially performed aiming to disintegrate all the ipsilateral stones. In patients with intrarenal stones, when the patency of the ureter had been achieved the treatment was proceeded with RIRS.

For ureteral stones a 8/9.5F semirigid ureteroscope (Richard Wolf GmbH) was used. Some stones in the

proximal ureter and all the renal ones were fragmented with a 4.9/7.95 F flexible ureteroscope (URFP6, Olympus). Lithotripsy was performed using a 30 W Litho Ho:YAG laser system (Quanta System), with 365 or 200 micron laser fibers. The system was adjusted in the dusting mode with frequency ranging from 5 to 15 Hz and energy between 0.2 and 2 J according to stone hardness. 10-12F access sheaths (Uropass, Gyrus Medical Ltd.) were used to facilitate the reinsertion of the flexible scope.

Larger stone fragments were removed with either a 1.8 or a 3F nitinol tipless basket (Ultra-Catch, Olympus Europa) and double j stent (djs) was left in place for 7-10 days upon suspicion for minor ureteral trauma. Should a more severe ureteral trauma was suspected the stent was left for 4-6 weeks. SFR was defined as no residual stone or a single stone <3 mm detected in unenhanced low dose CT scan performed 3 months after the procedure. The stone type was not formally examined in all the patients. Stone examination with infrared spectroscopy was performed only in younger patients and in those with frequent recurrences.

**Statistical analysis.** Data were analysed using Stata™ (Version 13.0 MP, Stata Corporation). The Shapiro-Wilk test was performed to test for normal distribution of continuous factors and the relevant results are given as mean ( $\pm$  SD) while not normally distributed variables are presented as median values [IQR]. Univariate and multivariate logistic regression analysis were applied in order to identify independent prognostic factors related to the outcomes. All tests were two-tailed and statistical significance was established at 5% ( $P < 0.05$ ).

## Results

**Patient characteristics.** Overall 237 stones were detected in 155 patients who consented on for both the proposed treatment and their inclusion in the study too, representing a mean burden of 1.5 stone per patient. Patients' characteristics are presented in Table I.

For the total group of patients the mean age was 58.02 years, with a limited number of female participants in the study (79 males vs. 76 females, ratio 1.04:1). 30 cases had a history of previous treatment. With a median total stone size of 12 mm the SFR1 of a single procedure was 80%. After a mean of 1.23 procedures per patient the SFRf was 94.2%. The overall complications' rate was 26.4%. Apart from lower urinary tract symptoms (LUTS) the list of complications included fever, hematuria, UTI with or without hospitalization, sepsis, ureteral trauma (but without ureteral avulsion events) and ureteral stenosis. Acute myocardial infarction was postoperatively diagnosed in one patient. Overall 15 patients experienced Clavien grade 3-4 complications (9.7%).

**Total group analysis.** In univariate analysis (Table II), total number of stones, presence of stone in the lower calyx, total stone size and preoperative stenting were factors correlated with SFR1. Total stone number, total stone size, number of stones in the ureter and kidney, presence of stones in the lower calyx and total stone size were correlated with the SFRf. In respect to the complications only age and total stone size were significant factors.

Table I. Patient characteristics.

Factor	Total group (n=155)	Group A (n=114)	Group B (n=41)	P-value
Age in years ( $\pm$ SD)	58.02 (13.69)	57.3 (14.31)	59.9 (11.72)	0.3075
Male sex, n (%)	79 (51)	55 (48.25)	21 (51.22)	0.856
Laterality (Rg=left), n (%)	75 (48.4)	54 (47.37)	21 (51.22)	0.718
HU (IQR)	780 [620-928]	816 [640-1050]	771 [544-910]	0.156
Type of intervention, n (%)				<0.001
F only	5 (3.2)	5 (4.39)	0 (0.00)	
SR only	93 (60)	84 (73.68)	9 (21.95)	
SR+F	57 (36.8)	25 (21.93)	32 (78.05)	
Total size in mm, median (IQR)	12 [8-17]	10 [7-15]	22 [16-32]	<0.001
Total number of stones (mean)	237 (1.52)	114 (1)	123 (3)	0.034
Number of ureter stones (mean)	192 (1.24)	114 (1)	80 (1.95)	NA
Number of kidney stones (mean)	44 (0.28)	0 (0%)	44 (1.07)	NA
Stone in lower calyx, n (%)	7 (4.5%)	0 (0%)	7 (17.1%)	NA
Stent preoperatively, n (%)	90 (58.1)	66 (57.9)	24 (58.5)	>0.999
Stent postoperatively, n (%)	127 (81.9)	93 (81.6)	34 (82.3)	>0.999
Access Sheath, n (%)	42 (27.1)	17 (14.9)	25 (60.9)	<0.001
Use of basket, n (%)	69 (44.5)	41(35.9)	28 (68.3)	<0.001
Operation time, mins (IQR)	60 [45-95]	57.5 [42-90]	88 [55-105]	0.002
Hospital Stay days (IQR)	1 [1-2]	1 [1-2]	1 [1-3]	0.308
SFR1, n (%)	124 (80)	94 (82.5)	30 (73.2)	0.255
Chemolysis, n (%)	4 (2.6)	1 (0.9)	3 (7.3)	0.057
Complication, n (%)	41 (26.4)	27 (23.7)	14 (34.1)	0.218
Clavien grade 3-4, n (%)	15 (9.7)	10 (8.8)	5 (12.2)	0.112
Sepsis, n (%)	11 (7.1)	8 (7)	3 (7.3)	0.435
Number of treatments, n (%)				0.757
1	128 (82.6)	95 (83.3)	33 (80.5)	
2	19 (12.3)	14 (12.3)	5 (12.2)	
3	8 (5.1)	5 (4.4)	3 (7.3)	
Total number of treatments (mean per patient)	186 (1.23)	138 (1.21)	52 (1.27)	
SFRf, n (%)	146 (94.2)	110 (96.5)	36 (87.8)	0.056

F, flexible; IQR, interquartile range; NA, non available; Rg, reference group; SD, standard deviation; HU, Hounsfield units; SFR1, stone free rate in one session; SFRf, final stone free rate (after all sessions); SR, semirigid.

Multivariate logistic regression analysis (Table III) revealed that preoperative stent placement and total stone size were independent prognostic factors for SFR1. For the end point of SFRf no independent prognostic factor was detected. Age, stone in the lower calyx and total stone size were independently associated with increased complications.

**Comparative analysis.** In 41 cases multiple stones were detected with a mean burden of 3 stones per patient (group B). The control group consisted of 114 cases with single ureterolithiasis (group A). The majority of patients of group B were treated with the combined SR and F endoscopic lithotripsy aided by the placement of access sheath while for group A SR endoscopy was more frequently implicated. The median lithiasic burden was higher (22 vs. 10 mm,  $P<0.001$ ) and the duration of intervention longer (88 vs. 57.5 min,  $P=0.002$ ) in group B compared with group A respectively. However, the median duration of hospital stay was similar (one day for each

group). After one lithotripsy procedure the SFR1 was similar for both groups (82.5 and 73.2% for group A and B respectively) ( $P=0.255$ ).

Likewise, neither the outcome of SFRf (96.5% vs. 87.8%) nor the mean number of procedures per patient (1.21 vs. 1.27) for the group B and A respectively were statistical significant different (Table I). Of the 5 treatment failures of group B, two hosted stones in the lower calyx.

## Discussion

ESWL is a safe and effective method of treating urinary stones of small and medium size, particularly those located in the upper urinary tract (8). However, for lithiasic burdens >20 mm located in the kidney the results of ESWL are compromised and the reported stone free rates are approximately 50-55% (9,12). Likewise, retrograde endoscopy and laser lithotripsy, either with flexible or semirigid scope, is the standard of care for

Table II. Univariate logistic regression models for the identification of factors related to SFR1, SFRf and overall complications for the total group of patients.

Outcome	SFR1			SFRf			Complications		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Sex (Rg=females)	0.75	0.34-1.65	0.470	0.76	0.19-2.93	0.687	1.32	0.65-2.71	0.444
Age	1.03	0.99-1.06	0.060	1.002	0.95-1.05	0.944	1.03	1.003-1.06	0.027
Laterality (Rg=left)	0.25	0.10-0.60	0.203	0.45	0.11-1.86	0.269	0.66	0.32-1.35	0.251
Total no. of stones	1.49	1.08-2.06	0.015	2.10	1.35-3.26	0.001	1.35	0.99-1.84	0.060
No. of ureter stones	1.57	0.99-2.49	0.055	1.94	1.12-3.37	0.018	1.47	0.93-2.31	0.096
No. of kidney stones	1.49	0.93-2.38	0.097	2.14	1.21-3.79	0.009	1.29	0.81-2.04	0.277
Stone in the lower calyx (Rg=no)	5.97	1.26-28.3	0.024	8.06	1.32-49.1	0.024	1.12	0.21-5.99	0.897
Total stone size	1.08	1.03-1.12	0.001	1.12	1.05-1.19	0.001	1.07	1.03-1.12	0.001
Stent preoperatively (Rg=no)	2.44	1.01-5.89	0.046	1.48	0.36-6.13	0.592	1.35	0.65-2.82	0.419

CI, confidence interval; OR, odds ratio; Rg, reference group; SFR1, stone free rate in one session; SFRf, final stone free rate (after all sessions).

Table III. Multivariate logistic regression models for the identification of independent factors related to SFR1 and complications.

A, SFR1					
Factor	OR	Std. Err.	z	P> z	95% CI
Stent preoperatively	0.2799494	0.1657261	2.15	0.032	0.0877365-0.8932622
Total stone size	0.9451793	0.0229961	-2.32	0.020	0.9011655-0.9913428
B, Complications					
Factor	OR	Std. Err.	z	P> z	95% CI
Age	0.032445	0.0158132	-2.82	0.037	1.001912-1.063908
Stone in the lower calyx	0.094723	0.1072088	-2.08	0.042	0.0103053-0.8706735
Total stone size	1.10058	0.0274499	-3.84	<0.001	1.048073-1.155717

CI, confidence interval; OR, odds ratio; SFR1, stone free rate in one session; Std. Err., standard error.

ureterolithiasis but it is still an option for intrarenal stones greater than >20 mm (3). In one of the most recent systematic reviews, the SFR was inferior but the hospital staying was shorter following flexible RIRS compared with PCNL (5). In the settings of large stones of the upper tract therefore, PCNL is the standard of care but at a cost of higher invasiveness and increased risk for complications particularly if multiple punctures are required (13,14).

In a high percentage of lithiasic patients, multiple stones may be encountered. In our study 41 out of 155 patients were diagnosed with multiple lithiasis corresponding to the rate of 26.4%. This figure is similar to the rates reporting in other series ranging between 20 and 25% (9). In the settings of multiple lithiasis, URS with or without RIRS could be considered for treating these patients (14,15). In a single arm analysis comprising patients with multiple stones two out of three cases (66.7%) were rendered stone free one month after a single flexible retrograde lithotripsy (16). Takazawa *et al* showed that for

a mean lithiasic burden of 21.5 mm, a figure similar to that of group B of the present study, the SFRs were 80 and 92% after the first and the second procedure respectively (8). In another report comprising patients with multiple nephrolithiasis, the SFR was as high as 100% for a total size of <20 mm compared with 84% in patients with larger sum of lengths (9). For stones <20 mm Breda *et al* reported a SFR of 79 and 100% after one and two procedures respectively (10). Among our patients of group B, with a median size of 22 mm and a median stone number of 3, the initial and final SFR was 73.2 and 87.8% respectively which compare well with the aforementioned reports.

As it is shown in Table III, in multivariate analysis the total stone size and the presence of ureteral stent were independent prognostic factors for SFR1. This means that neither the number nor the location of stones in the collecting system had a significant influence on the results of the first lithotripsy and the physician should not be discouraged from proposing

and offering retrograde lithotripsy to the patients with multiple and/or large stones, particularly to those with pre-stented ureters. It could also be supported that the modern lithotripsy scopes and laser devices enables for an effective and safe treatment of multiple stones and of larger lithiasic burdens compared with the past.

Moreover, for the end point of SFRf no significant predictive factors were revealed. It seems that the first lithotripsy enhanced the results of subsequent or auxiliary session maximizing the stone clearance effect. The djs, which was placed in almost 60% of the patients before the first lithotripsy, was then present in all the ureters before the second procedure, facilitating thus the outcome of the reoperation. Although the lower calyx lithiasis was correlated with the SFRs in univariate analysis, this variant proved to be an independent prognostic factor only for complications in multivariate settings. In other words, the presence of stones in the lower calyx was not independently associated with the stone clearance. It seems that the modern flexible endoscopes and the more sophisticated laser devices enables for favorable SFR outcomes of lower pole lithiasis. The aforementioned reasons, combined with the limited rate of patients (20%) registered for reoperation, could be the plausible explanations for the lack of significant prognostic factors for the end point of SFRf.

Increased age, large total lithiasic burden and/or stones in the lower calyx were independently associated with increased complications. It seems that older patients are more vulnerable, compared with the younger population. Older patients are prone in developing postoperative LUTS, infections and fever probably due to their aging urinary tract system and the increased volume of the prostate in male patients. Perhaps in the elderly the previous exposure to bacteria and the delayed mucosal healing after a minor trauma are both related with increased complications rate. Therefore, careful manipulations of the instruments, avoidance of high pressure irrigation and minimum operation time are issues that could be followed for diminishing complications. These patients should be informed about the increased odds of complications before signing the informed consent and should be treated with caution irrespectively of the number of detected stones or the presence of double j stent.

Our report is one of the few studies to investigate prognostic factors for the outcomes of retrograde lithotripsy. Similar to our findings, Lee *et al*, by using the threshold of 100 mm<sup>2</sup>, revealed that the cumulative stone burden was an independent prognostic factor for the one-month SFR. They also did not reveal any correlation with the stone number or their location in the urinary tract (16). Lai *et al* reported lower rates of complications in pre-stented patients with renal calculi (15), a finding that is not confirmed in the present study though.

At the second stage of our study, emphasis was given on the comparison of the outcomes of multiple lithotripsy (group B) vs. single URL as the standard of care (group A) (Table II). As expected, the median duration of operation was longer for multiple lithiasis by approximately 30 min. However, this duration (88 min) is reasonable considering that in other reports with similar or lower lithiasic burden the mean operative time ranges between 72 and 112 min (8,15,16).

More importantly, we sought to determine whether the prolonged operation time and the need for multiple re-insertions of instruments may increase the rate or severity of complications. This hypothesis is not confirmed in the present analysis. The overall complications' rate were higher for group B compared to A (34.15% vs. 23.7% respectively) but it was not of statistical significance ( $P=0.218$ ). Likewise, no impact on duration of hospital staying was recorded for the group of multiple stones (median value: one day for either group A or B,  $P=0.3081$ ). Although logistic regression analysis was not feasible for severe Clavien grade  $\geq 3$  complications and for sepsis, the rate of this outcome was also similar between the groups confirming the safety of multiple lithotripsy. In addition, ureteral stenosis and trauma were also rarely encountered (in one patient of group B and in two others of group A).

Reviewing the literature, the rate of adverse effect range between 5% (14,16) and 23% (12,15) for retrograde lithotripsy. Comparatively, in the present study higher rates of complications (23.7 and 34.1% for group A and B respectively) are revealed. These finding could be attributed mainly to the inclusion of lower urinary tract symptoms (LUTS) in the list of complications. Should LUTS are excluded from analysis the complication rates for group A and B were much lower (22 and 18% respectively).

Compared to single fragmentation, the multiple lithotripsy procedure yielded inferior results for the end points of initial and final SFR respectively. These differences are however not of statistical significance ( $P=0.255$  and  $0.056$  respectively) indicating that the outcomes are not compromised in group B. The total number of procedures per patient were also similar between the two groups (1.21 vs. 1.27 for group A and B respectively,  $P=0.757$ ) which also confirms the merit of multiple lithotripsy. As it was mentioned previously, in multivariate analysis the total stone size was not an independent prognostic factor for SFRf. In other words, although flexible RIRS is not considered the standard of care for large stones, it could still be an attractive treatment for multiple stones including the renal ones, indicating a shift of the treatment paradigm from PCNL towards an even less invasive procedure for stones with sizes even larger than 20 mm.

We used access sheath in the majority of patients with large stones; it facilitated the insertion of the flexible scopes, in removal of stone fragments and to shortening of the operation time. More importantly, access sheath may prevent excessive increase of intrarenal pressure within the pelvis during prolonged fragmentation. In a multicenter trial, concerns were raised about ureteral injury after access sheath placement in the settings of large lithiasic burden (17) but they were not confirmed in the present study. Injury of the ureter was recorded in 2 patients; in only one of them the injury was associated with placement of access sheath. In another patient, ureteral stenosis was diagnosed shortly after the removal of djs and a ureteral stent was reinserted. In this patient access sheath was not used though. It should be emphasized however that the comparison between patients with single or multiple lithiasis should be made with caution considering that the preoperative characteristics regarding the stone size and location were not similar between A and B group. The number of patients registered in each group was also dissimilar raising some concerns about the risk of bias following the comparison

of the postoperative results. Moreover, the length of the stone might not be the ideal index of the stone burden, considering that this parameter is better represented by the stone surface or the volume after 3D reconstructions of the CT slices. Nevertheless, several authors (6,8-10) have clearly defined and used the sum of maximum diameters of the stones as a surrogate for the total stone burden. This methodology was also applied in the present manuscript too. We also acknowledge that a larger study population particularly in the group of multiple lithiasis would be preferable for safer and more robust outcomes to be extracted. All the aforementioned are considered as limitations of the study.

Despite the limitations of the study, by using logistic regression analysis, plausible prognostic factors for the likelihood of stone clearance and for the odds of complications were revealed. Older patients with higher burdens and stones in the lower calyx should be treated with caution. It was also shown that for sizes up to 22 mm, the performance of URL with or without RIRS is optimal against multiple stones irrespective to their location, albeit more scientific evidence is required. Patients with larger burdens could also experience benefit though, by reducing the need for auxiliary treatments or enhancing the outcome of any subsequent procedure.

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### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Authors' contributions

DKo and ZK confirm the authenticity of all the raw data. DKo and GS conceived the study, and ZK and KS contributed to the study design. DKa and AZ performed the experiments and collected the raw data. SP, SEC, IK and NM contributed equally to the analysis and interpretation of the results. ML participated in the analysis and interpretation of data. KS, ML and NM wrote and reviewed the manuscript. DKo, ML and ZK performed a literature review. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

Prior to any treatment, all participants were informed about the treatment options available for single and multiple lithiasis. Detailed information was provided about the results and complications of retrograde ureterolithotripsy and retrograde intrarenal surgery. Patients who accepted the details provided written informed consent. The methods of treatment meet the criteria of Helsinki declaration for human rights and the study was approved by the General Hospital of Volos Ethics Committee (protocol no. 3718/17-3-2017).

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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