Original Article

When should we give up on expectant management for patients with proximal ureteral stones?

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Abstract

Background: Proximal ureteral stones (PUS) have relatively low rates of spontaneous expulsion. However, some patients do well on expectant management. Our aim was to compare risk factors for surgical intervention in patients with PUS who underwent primary intervention to those subjected to expectant management.

Materials and methods: We retrospectively reviewed the medical charts of patients presented to the emergency room with symptoms of renal colic and underwent computerized tomography between August 2016 and August 2017. A total of 97 consecutive patients were identified with up to 10 mm PUS. We collected patient demographics, clinical, and imaging data, and performed binary regression analysis for risk of intervention.

Results: The average age was 49 years (range 17–97) and average stone size was 7.1 mm (range 3–10). Forty-one patients underwent immediate intervention while the remaining 56 patients were treated conservatively. Of the 56 patients treated conservatively, 26 underwent delayed intervention while 30 reported spontaneous stone expulsion. On univariate analysis of all 97 patients, statistically significant risk factors for intervention were found based on stone size, age, serum lymphocyte, platelet counts, and stone density. Of these risk factors, stone size ≥ 7 mm ($p = 0.012$, odds ratio $= 5.4$) and platelet count ≤ 230 K/µL ($p = 0.027$, odds ratio $= 4.9$) remained statistically significant on multivariate analysis.

Conclusion: Stone size and platelet count were found to be risk factors for surgical intervention in patients with up to 10 mm PUS. These findings may assist in identifying patients who are more suitable for conservative approach.

Keywords: Nephrolithiasis; Renal colic; Ureteral calculi; Ureterolithiasis; Urolithiasis

1. Introduction

Ureteral calculi are commonly associated with excruciating pain, renal failure, and infection, and they are a major cause for visits to the emergency room (ER).[1] While surgical intervention is necessary for some patients, expectant management is a valid option for others when invasive urologic procedures and anesthesia can be obviated. In the absence of mandatory indications for intervention, expectant management is often selected for patients with small and distal ureteral stones (DUS), as spontaneous stone passage is frequent in up to 80% of cases.[2–7] Conversely, proximal ureteral stones (PUS) impose a more difficult clinical decision because of a much lower stone passage rate.[5,6] Identification of risk factors for surgical intervention may be helpful in clinical decision-making and correct selection of patients with a good likelihood of passing PUS as opposed to others who will likely need a procedure. Such risk stratification will benefit both groups as it could save invasive

procedures in patients who will eventually pass the stone and save time in hospital, loss of labor days, and pain from those who are unlikely to have stone passage. To determine which risk factors could predict the endpoint of need of surgical intervention, we retrospectively analyzed the charts of patients with PUS at our center.

2. Materials and methods

Following approval of the local institutional review board, we retrospectively reviewed all patients presented to our ER with renal colic, who underwent non-contrast computer tomography (CT) between August 2016 and August 2017. Only patients diagnosed on CT scan with ureteral stone proximal to the common iliac vessels were included in the study. We excluded patients with more than a single stone in the ureter, < 18 years of age, fever over 38°C, or with stones larger than 10 mm. Demographic, clinical, laboratory and imaging data were collected from the medical files and listed in Table 1.

Imaging data were collected from computerized software "PACS" (version 11) and included stone size, level of hydronephrosis, stone density, rim sign and stone distance from iliac vessels (mm). Stone size was measured in all three views — coronal, sagittal and axial — and the coronal stone size was eventually selected as it measured the largest stone size of all three views. Stone density was measured in Hounsfield units as a circular region of interest located completely within the stone and covering more than 50% of the entire stone area. Distance of each stone from the iliac vessels was measured on the coronal view,

Table 1

Univariate analysis of demographic, clinical, laboratory, and radiographic variables.

Variables	All patients	Intervention	Expectant management	p
Gender				
Male	83 (85.6%)	57 (85.1%)	26 (86.7%)	0.84
Female	14 (14.4%)	10 (14.9%)	4 (13.3%)	
Age, yr, mean (SD)	49 (14)	52 (14)	44 (13)	0.015
Symptom duration, d, mean (SD)	4 (13)	4.8 (15)	2.2 (2)	0.04
Side				
Right	42 (43%)	29 (43%)	13 (43%)	
Left	55 (57%)	33 (57%)	17 (57%)	
Stone density, Hounsfield units, mean (SD)	900 (351)	971 (348)	740 (308)	0.002
Stone size, mm, mean (SD)	7.2 (1.9)	7.8 (1.8)	5.8 (1.5)	<0.001
Distance from iliac vessels, mm, mean (SD)	77.5 (28)	77.6 (29)	77.2 (27)	0.756
Hydronephrosis				
None/mild	65 (67%)	43 (64%)	22 (73%)	0.223
Moderate/severe	32 (33%)	24 (36%)	8 (27%)	
WBC, K/μL, mean (SD)	11.1 (3.2)	11 (2.9)	11.3 (2.9)	0.69
Lymphocytes, K/μL, mean (SD)	1.8 (0.8)	1.7 (0.7)	2.0 (0.9)	0.03
Platelets, K/μL, mean (SD)	234 (76)	217 (55)	272 (100)	0.001
Creatinine, mg/dL, mean (SD)	1.27 (0.44)	1.32 (0.5)	1.16 (0.3)	0.147

SD = standard deviation; WBC = white blood cell.

where both stone and blood vessels were visible. The initial 10 CT scan images were reviewed by a resident and senior urologist to confirm unity in data collection. An additional 5 CT scans were analyzed initially by the resident and adequate data collection was confirmed by the senior urologist.

The decision of whether to intervene or not was taken in the majority of the cases as a group decision, rather than per each attending physician, and followed general considerations including intractable pain, renal failure, abnormal blood tests, or deterioration in general condition. The type of surgical intervention was selected by the attending physician, following department and hospital preferences. The cohort was divided into patients who required intervention, including primary ureteroscopy, ureteral stent insertion or nephrostomy tube insertion, and patients selected for conservative management with successful stone expulsion. We suggest that from a chronological point of view, a decision to intervene surgically should be based on presurgical data rather than postsurgical data, so that the type of surgery was not assessed as a risk factor for intervention.

Patients were considered as undergoing successful stone expulsion after follow-up visits demonstrated no abnormal radiological findings on renal ultrasound, with no relevant clinical findings, or if the patient brought the expelled stone that corresponded to the imaging size.

Statistical analysis was performed using a single-variable analysis and a multivariate analysis using logistic regression. Variables of both groups were compared using t test or Mann–Whitney for continuous variables and chi-square for categorical variables. Cut-off points for continuous variables were selected after plotting receiver operating characteristics curves. Values of $p < 0.05$ were considered statistically significant. Calculation of statistical tests was performed using SPSS version 21.

3. Results

We examined files of 138 consecutive patients who were admitted to the ER for renal colic between August 2016 and August 2017 and diagnosed with PUS. Of the 138 patients,

41 were excluded due to a stone size larger than 10 mm or lack of follow-up information, yielding 97 patients as the final cohort. Of the 97 patients, 41 underwent primary surgical intervention. The remaining 56 patients were treated via expectant management; 30 (54%) patients reported spontaneous stone expulsion while 26 (46%) patients underwent delayed surgical intervention.

We divided the 97 patients into 2 groups: group 1 with 67 patients (69%) who required surgical intervention, either primary or delayed, and group 2 with 30 patients (31%) who were managed successfully with conservative treatment and reported spontaneous stone expulsion (Fig. 1). The demographic, clinical, laboratory and imaging variables of the entire cohort and 2 groups are shown in Table 1.

A univariate analysis was performed between the groups, and the following characteristics were noted to be statistically significant: age, duration of symptoms, stone size, stone density, lymphocytes, and platelet count (Table 1). Multivariate analysis showed that stone size (odds ratio [OR] = 5.4, 95% confidence interval = 1.44–20.1, $p = 0.012$) and platelet count (OR = 4.9, 95% confidence interval = 1.19–20, $p = 0.027$) remained statistically significant between the groups (Table 2). Receiver operating characteristics analysis revealed the following cut-off values for stone size and platelet counts: stone size >7 mm (OR = 5.4, $p = 0.012$) and platelet count <230 K/μL (OR = 4.9, p = 0.027), both of which are associated with an increased risk for intervention (Fig. 2).

Assessing the significant risk factors (stone size >7 mm and platelet counts <230 K/μL) on the entire cohort, we found that patients with 0, 1, and 2 risk factors had 15%, 45%, and 88% likelihood of undergoing surgical intervention, respectively (Fig. 3).

4. Discussion

Patients with PUS represent a treatment challenge for the urologist. While expectant management may be an appealing decision omitting the need for surgical intervention, the majority
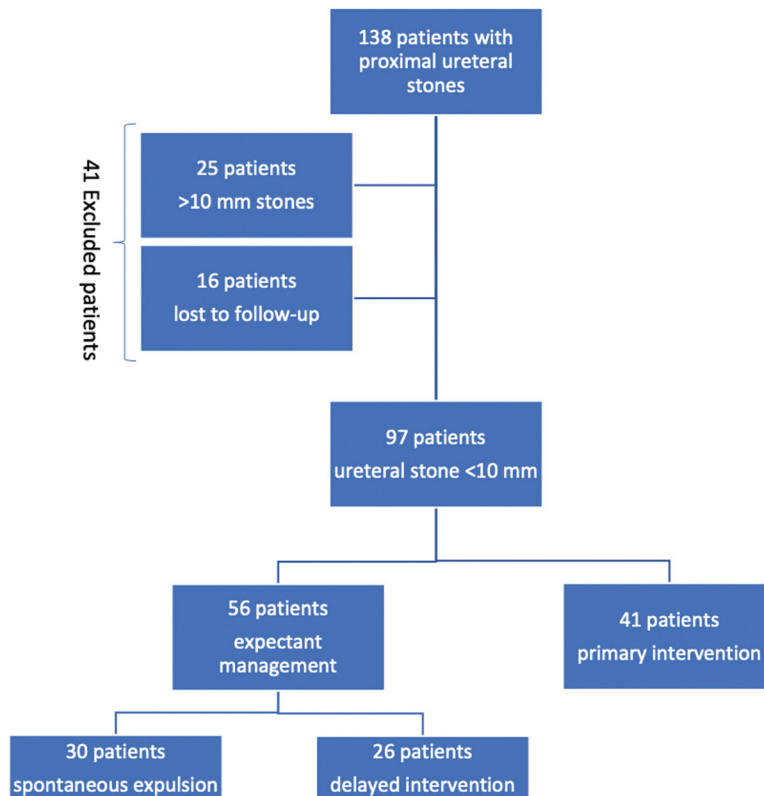
Figure 1. Schematic algorithm of patient management.

of patients will not pass the stone spontaneously. We note that while 30% of our patients were able to pass the stone spontaneously, nearly 70% of the patients required surgical intervention. These results are the opposite of those regarding successful conservative management versus surgical intervention of DUS.[8] Despite medical literature[5] reporting high rates of surgical intervention of up to 70%, a substantial number of patients with PUS will do well on expectant management. We therefore searched for clinical parameters that will identify patients indicating high likelihood to pass a proximal stone spontaneously.

Univariate analysis showed that age, stone size, and density, duration of symptoms, and inflammatory markers such as white blood cells (WBC) and platelets are statistically different between patients who required surgical intervention and those

who did not. Multivariate analysis showed only stone size and number of platelets remained significantly different between the groups.

Ureteral stone size is a well-established predictor of spontaneous stone expulsion as mentioned in previous studies.[4,5,7,9,10] More specifically, and in accordance with our findings, Coll et al.[4] reviewed the relationship between stone size and spontaneous expulsion in 172 patients with ureteral stones. Sixty-two of the patients had PUS, of whom only 25% with stones larger than 7 mm passed the stone spontaneously; more than 60% of the patients with ureteral stones of size 5–7 mm passed them spontaneously. The mean stone size for our PUS patients was 7.2 mm, with passage rates of 30%, which is similar to the 25% rates reported for PUS stones larger than 7 mm in Coll et al.[4] On the other hand, Ye et al.[10] showed that most DUS larger than 5 mm will pass either spontaneously or with medical expulsive therapy in a rate ranging between 75% and 87%, respectively. In the MIMIC study,[11] 40% of patients with over 5 mm PUS were successfully treated with conservative management, emphasizing again the importance of detecting patients who are less likely to pass the stone based on parameters other than stone size.

Given that stone size appears to play a major role, the question arises as to why a 7 mm stone located in the upper ureter has lower rates of spontaneous expulsion than a similar 7 mm stone in the lower ureter. The answer is not clear, as any 7 mm DUS must have advanced through the upper ureter first—yet is more likely to pass spontaneously. Therefore, it is likely that stone size, while as a key factor for stone expulsion, does not reflect other important factors. Such factors may include anatomical parameters like stone surface area, morphology, and roughness.

Table 2

Multivariate analysis of variables found to be significantly different on univariate analysis.

Variables	Univariate analysis	Multivariate analysis	
	p	p	OR (95% CI)
Age	0.015	0.16	
Symptom duration	0.04	0.08	
Stone size	<0.001	0.012	5.4 (1.4–20.2)
Stone density	0.002	0.87	
Lymphocyte count	0.03	0.97	
Platelet count	0.001	0.027	4.9 (1.2–20)

CI = confidence interval; OR = odds ratio.
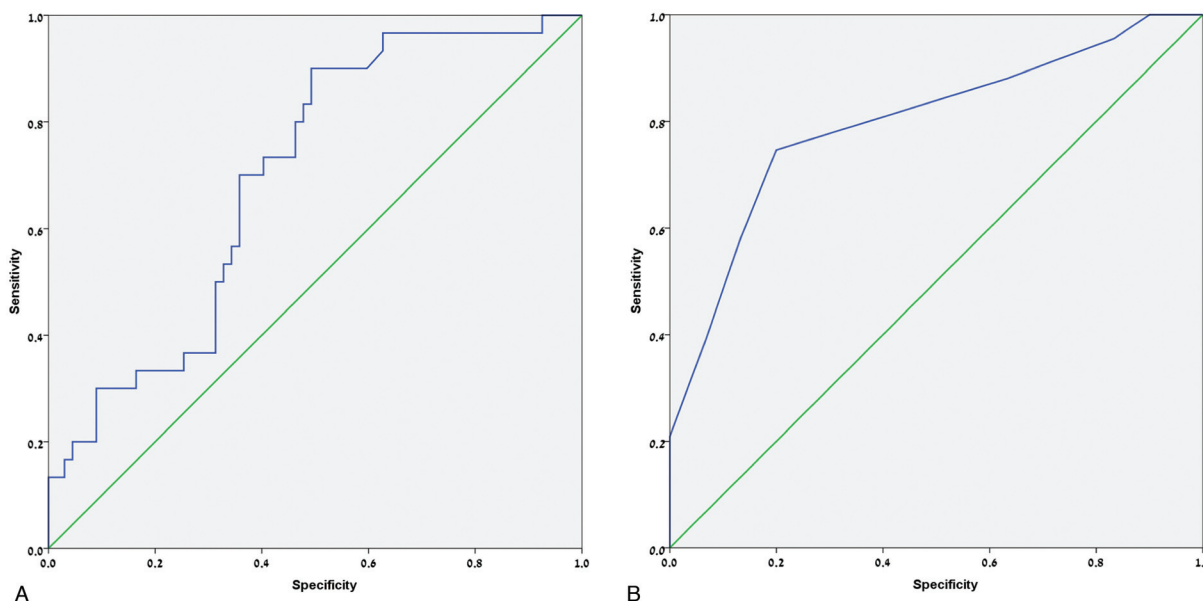
Figure 2. Receiver operating characteristics curve analysis of risk factors: stone size (upper plot) and platelet count (lower plot).

Indeed, stones located in the distal ureter may reflect a favorable interaction between the stone and ureter, as well inherent ureteral characteristics such as elasticity and inner diameter. There is evidently a process of selection wherein characteristics of stones able to reach the distal ureter are in general more amenable to spontaneous expulsion.

Based on the fact that DUS tend to pass more easily than proximal ones, we assessed the location within the proximal part of the ureter by measuring the distance between the stone and iliac vessels. We were unable to detect any significant correlation between the location within proximal ureter and the likelihood of passing a stone.

Another possible explanation for failed expectant management is an inflammatory ureteral reaction to stone presence, which may lead to impaction and ureteral stenosis. We therefore searched for inflammatory mediators that may play a role in such an interaction. An inverse interaction was indeed noted between platelet count and intervention risk. Patients with platelet count $<230 \, K/\mu L$ had higher intervention risk. The exact mechanism in which lower platelet counts contribute to higher rates of intervention is unclear. A possible explanation may be that patients who are more symptomatic consume larger amounts of pain medication that carry the risk of lowering platelet counts.
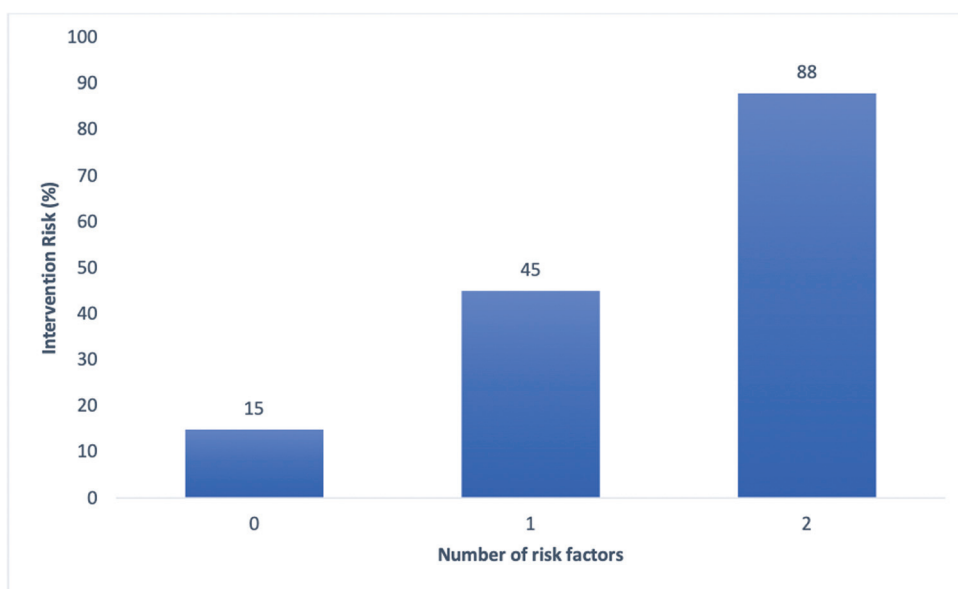
Figure 3. Intervention risk according to risk factors.

Other authors have attempted to correlate inflammatory markers and stone passage.[6,7,12,13] Shah et al.[11] conducted a multicenter retrospective analysis assessing the effect of inflammatory markers in patients with ureteral stones. They reported that C reactive protein (CRP), WBC and neutrophil count have no predictive value for stone expulsion.[14] Ozcan et al.[6] prospectively evaluated 251 patients with DUS and found that patients who did not spontaneously expel ureteral stones had higher CRP levels and WBC counts. On the other hand, Jendeberg et al.[8] found no correlation between CRP levels and expulsion rate. Sfoungaristos et al.[9] prospectively evaluated patients with ureteral stones and noted that higher expulsion rates correlated to lower WBC count. We also assessed WBC counts, as well as lymphocyte counts, but were unable to detect any effect on stone passage.

A recent article[15] that aimed to identify risk factors for expulsion of DUS demonstrated that symptom durations longer than 4 days predicted the need for surgical intervention. Similarly, Bajaj et al.[14] examined 527 patients with renal colic, initially treated conservatively, and found that patients with symptoms >3 days are at significant risk for intervention. Here, we assessed the same parameter — symptom duration — for patients with PUS, but noted a significant difference only on univariate analysis but not on multivariate analysis.

When combining the two risk factors of stone size > 7 mm and platelet count <230 K/µL, the risk of surgical intervention was nearly 90%. On the other hand, in the absence of these risk factors, the intervention risk was as low as 15%. These findings may assist in setting expectations and relevant treatment options during informed consent. For example, a patient with 8 mm PUS and platelet count of 200,000 is far more likely to undergo surgical intervention as compared to a patient with a 5 mm PUS and platelet count of 300,000. Clearly, a faster decision to intervene surgically may omit readmission rate, loss of work days and consumption of pain medication.

This study has several limitations due to its retrospective nature. In particular, the decision to intervene surgically lacked standardization and potentially led to selection bias. However, it is noted that our surgical ward includes five senior attending urologists who favor different treatment approaches; this variation at least potentially minimizes biased surgical intervention. Another limitation is that this analysis reflects our own treatment decisions, which may not be in accordance with other urological centers. While our approach may differ from other urologists, the rate of intervention in our study is similar to rates quoted by most studies that evaluated conservative treatment for ureteral stones. Finally, we have no information regarding stone composition, which may be valuable in terms of stone factors that may be more favorable to either expulsion or impaction. Of note however, is the fact that we did assess stone density on noncontrast CT, which correlated with stone composition, and found no relationship to surgical intervention on multivariate analysis.

5. Conclusion

With the rise in prevalence of nephrolithiasis, a substantial medical and financial burden is placed on the health system. Patients with PUS, for whom the rate of spontaneous stone expulsion is relatively low, are prone to be negatively affected by expectant management, including higher consumption of analgesics, readmission rates and loss of work days. Therefore, risk stratification may be valuable for treatment decisions regarding whether or not to intervene surgically. In conclusion,

we found that stone size and platelet count play a significant role in determining the likelihood of requiring surgical intervention and omitting the burden of failed expectant management. Further prospective studies, preferably randomized controlled trials following standardized criteria for treatment decision, are required to further validate these findings.

References

[1] Hyams ES, Korley FK, Pham JC, Matlaga BR. Trends in imaging use during the emergency department evaluation of flank pain. *J Urol* 2011;186(6):2270–2274.

[2] Preminger GM, Tiselius HG, Assimos DG, et al. Guideline for the management of ureteral calculi. *Eur Urol* 2007;52(6):1610–1631.

[3] Kambadakone AR, Eisner BH, Catalano OA, Sahani DV. New and evolving concepts in the imaging and management of urolithiasis: Urologists' perspective. *Radiographics* 2010;30(3):603–623.

[4] Coll DM, Varanelli MJ, Smith RC. Relationship of spontaneous passage of ureteral calculi to stone size and location as revealed by unenhanced helical CT. *AJR Am J Roentgenol* 2002;178(1):101–103.

[5] Pickard R, Starr K, MacLennan G, et al. Medical expulsive therapy in adults with ureteric colic: A multicentre, randomised, placebo-controlled trial. *Lancet* 2015;386(9991):341–349.

[6] Ozcan C, Aydogdu O, Senocak C, et al. Predictive factors for spontaneous stone passage and the potential role of serum C-reactive protein in patients with 4 to 10 mm distal ureteral stones: A prospective clinical study. *J Urol* 2015;194(4):1009–1013.

[7] Aldaqadossi HA. Stone expulsion rate of small distal ureteric calculi could be predicted with plasma C-reactive protein. *Urolithiasis* 2103;41:235–239.

[8] Jendeberg J, Geijer H, Alshamari M, et al. Size matters: The width and location of a ureteral stone accurately predict the chance of spontaneous passage. *Eur Radiol* 2017;27(11):4775–4785.

[9] Sfoungaristos S, Kavouras A, Perimenis P. Predictors for spontaneous stone passage in patients with renal colic secondary to ureteral calculi. *Int Urol Nephrol* 2012;44(1):71–79.

[10] Ye Z, Zeng G, Yang H, et al. Efficacy and safety of tamsulosin in medical expulsive therapy for distal ureteral stones with renal colic: A multicener, randomized, double-blind, placebo-controlled trial. *Eur Urol* 2018;73(3):385–391.

[11] Shah TT, Gao C, Peters M, et al. Factors associated with spontaneous stone passage in a contemporary cohort of patients presenting with acute ureteric colic: Results from the multi-centre cohort study evaluating the role of inflammatory markers in patients presenting with acute ureteric colic (MIMIC) study. *BJU Int* 2019;124(3):504–513.

[12] Park CH, Ha JY, Park CH, et al. Relationship between spontaneous passage rates of ureteral stones less than 8 mm and serum C-reactive protein levels and neutrophil percentages. *Korean J Urol* 2103;54(9):615–618.

[13] Lee KS, Ha JS, Koo KC. Significance of neutrophil-to-lymphocyte ratio as a novel indicator of spontaneous ureter stone passage. *Yonsei Med J* 2017;58(5):988–993.

[14] Bajaj M, Yuan L, Holmes LC, et al. Predictors of surgical intervention following initial surveillance for acute ureteric colic. *World J Urol* 2018;36:1477–1483.

[15] Modai J, Avda Y, Shpunt I, et al. Prediction of surgical intervention for distal ureteral stones. *J Endourol* 2019;33(9):750–754.