



Can ureteral wall thickness (UWT) be used as a potential parameter for decision-making in uncomplicated distal ureteral stones 5–10 mm in size? A prospective study

Mohamed Samir¹ · Hossam Elawady¹ · Emad Hamid² · Ahmed Tawfik¹

Received: 1 August 2020 / Accepted: 25 January 2021

© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2021

Abstract

Objective To evaluate the correlation between ureteral wall thickness (UWT) and stone passage (SP) and its cut-off value in distal uncomplicated ureteral stones.

Patients and methods In the prospective study from January 2019 to January 2020 at a tertiary care hospital, we reviewed 212 patients aged above 18 years with single, symptomatic, radiopaque, and distal ureteric stone sized 5–10 mm, who were treated with MET (Silodosin 8 mg once daily) until SP or a maximum of 4 weeks. There were 2 groups: responders and non-responders. Demographic data of the patients and all stone radiological parameters including stone size, laterality, density, UWT, the diameter of the ureter proximal to the stone (PUD), and the degree of hydronephrosis were recorded and compared between the 2 groups.

Results There were 126 (59.4%) in the responder group and 86 (40.6%) in the non-responder group. On univariate analysis, gender, stone density, stone size, PUD, UWT, and the degree of hydronephrosis were significant factors for stone passage. However, using multivariate analysis, only UWT and the degree of hydronephrosis were significant. ROC analysis showed that 3.75 mm is the cut-off value for UWT, with 86% and 87.3% sensitivity and specificity, respectively.

Conclusions UWT and hydronephrosis can be used as potential predictors for SP and can help with decision-making in patients with uncomplicated 5–10 mm lower ureteric stones.

Keywords Ureteral wall thickness · Lower ureteric stone · Medical expulsive therapy

Introduction

Urolithiasis is one of the most common diseases; 5–10% of the general population complain of urolithiasis [1]. Ureteral stones represent 20% of urinary tract stones and distal ureteral stones represent 70% of all ureteral stones [2].

MET (medical expulsive therapy) prescription has been under controversy for lower ureteric stone. However, according to the guidelines, patients with uncomplicated ureteral stones of ≤ 10 mm should be offered conservative treatment for 4–6 weeks [3]. During this period, patients may complain of recurrent colic and urinary tract infection (UTI) [4]. Therefore, differentiating between patients with ureteral stones who would benefit from conservative treatment or immediate interventions is crucial.

Clinical use of a significant non-invasive parameter to predict stone expulsion is important as it may decrease the unnecessary use of (MET) for the time during which the patient's quality of life is affected by the stone-bothering symptoms and the unpredictable alterations that occur in the upper urinary tract [5].

Stones cause inflammation in the ureteral mucosa, resulting in edema and fibrosis [6]. These inflammatory changes may lead to the failure of spontaneous passage of the stone

✉ Ahmed Tawfik
Murmur_urology26@hotmail.com

Mohamed Samir
m.samir-84@hotmail.com

Hossam Elawady
Dr_el3awady@hotmail.com

Emad Hamid
emadhamid@yahoo.com

¹ Urology Ain Shams University, Cairo, Egypt

² Ain Shams University, Cairo, Egypt

or of active treatment modalities such as ureteroscopy (URS) or shock wave lithotripsy (SWL) [7].

Recently, ureteral wall thickness (UWT) has been used to predict the results of (SWL). With the same token, UWT can possibly be a way to predict ureteric stone impaction during (URS) [8, 9]. However, there are limited data discussing UWT as a possible factor in predicting stone expulsion rate after MET [1].

To our knowledge, there is limited data to define the association of UWT and distal ureteric stone expulsion. The primary endpoint was to assess the role of UWT and its cut-off value in predicting stone passage and the secondary one was to evaluate other parameters of non-contrast spiral CT (NCCT).

Patients and methods

Patients

From January 2019 to January 2020, this prospective study was carried out at a single tertiary care hospital. Approval from the ethical committee of our institution was obtained before the start of the study. The inclusion criteria included patients aged above 18 years with single, symptomatic, radiopaque, and distal (below the sacroiliac joint) ureteric stone ranging in size from 5 to 10 mm. Exclusion criteria were patients with a solitary kidney, bilateral ureteric stones, intractable pain, renal impairment, (UTI), any congenital urologic anomalies, previous history of ureteral surgery, and whether the stone was located at the ureterovesical junction as in that case, the UWT could not be calculated.

A written informed consent was obtained from all patients after explaining the study procedures and the possible side effects. The patients were given silodosin 8 mg once daily until stone expulsion or a maximum of 4 weeks. Patients were assessed by history-taking, general examination, serum creatinine, urine analysis, urine culture, plain X-ray kidney, ureter and bladder (KUB), and NCCT. Patients were instructed to filter their urine to detect any passed stones.

A total of 775 patients with distal ureteric stones were assessed for eligibility. 339 patients were excluded for different reasons: 268 patients did not meet the inclusion criteria and 54 refused to participate, while 17 did not enter the study for other reasons, as shown in (Chart 1).

All patients underwent NCCT using a high-speed 64 MSCT helical Toshiba®. Patients were scanned from their diaphragm to symphysis pubic and the following parameters were used: 1.25 mm thickness, 0.625 mm interval, and 512×512 matrix with 1.75:1 pitch number. A rotation time of 0.5 s was used with a tube speed of 35 mm/rotation. The KV was 120, while the mA ranged from 120 to 400 according to body weight.

All NCCT images were evaluated manually by moving cursors from one point to another and independently by a radiologist. The stone and its surrounding tissue were assessed based on axial NCCT images with soft-tissue radiodensity (width, 350; level, 50). The pre-defined soft-tissue window had good tissue contrast for accurate measurement of the ureteral wall thickness, and detection of peri-ureteric edema.

The axial diameter of the stone and their density using Hounsfield units (HU) were measured. The UWT was measured as the point of greatest soft-tissue thickness (ureteral wall ± peri-ureteral edema) around the circumference of the stone; this evaluation ranged from the top to the bottom of the stone (Fig. 1).

The degree of hydronephrosis was assigned a value of 0–3.

A radiologist, blinded to the clinical outcomes, evaluated all NCCT films separately.

Follow-up protocol

Follow-up was performed weekly for up to 4 weeks at the outpatient clinic by history-taking, serum creatinine, urine analysis, ultrasonography, and KUB until spontaneous stone expulsion or no SP after 4 weeks of the treatment. Responders were defined as being stone-free in the follow-up KUB initially and NCCT if there was any suspicion, and non-responders as having residual stones in the former imaging studies after 4 weeks.

The demographic data of the patients, including age, gender, body mass index (BMI), and all stone radiological parameters extracted from NCCT such as stone size, laterality (right/left) and density using HU, UWT, diameter of the ureter proximal to the stone (PUD), and the degree of hydronephrosis (0–3) were recorded and compared between responders and non-responders.

Data management and analysis

Sample size was calculated using MedCalc Statistical Software version 15.8, setting the type-1 error (α) at 0.05 and the power ($1-\beta$) at 0.8. Results from Yoshida et al. showed that the ROC analysis for UWT in prediction of SP of stone had an accuracy of 0.83 (area under the curve of 0.83), and estimated 60% of the cases to pass the stone. Based on these values, a sample size of 120 cases will be needed to detect a difference of 0.13 between the area under the ROC curve (AUC) under the null hypothesis of 0.7 and an AUC under the alternative hypothesis of 0.83, taking into account a 20% drop out rate [1].

Data were revised, coded, entered on a computer, and analyzed using SPSS package version number 20. Quantitative data were described as mean, standard deviation

Chart 1 Consort flowchart

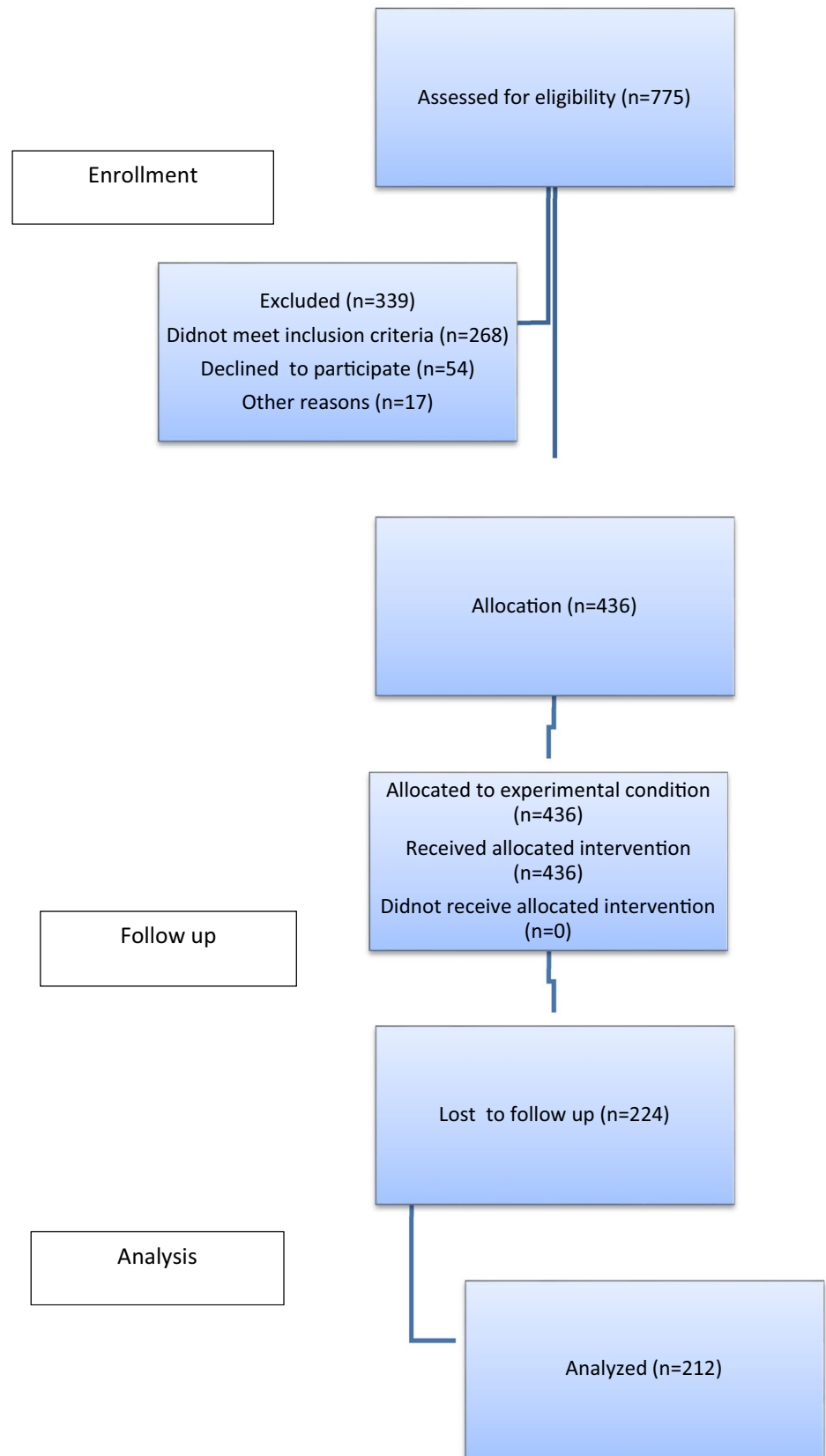
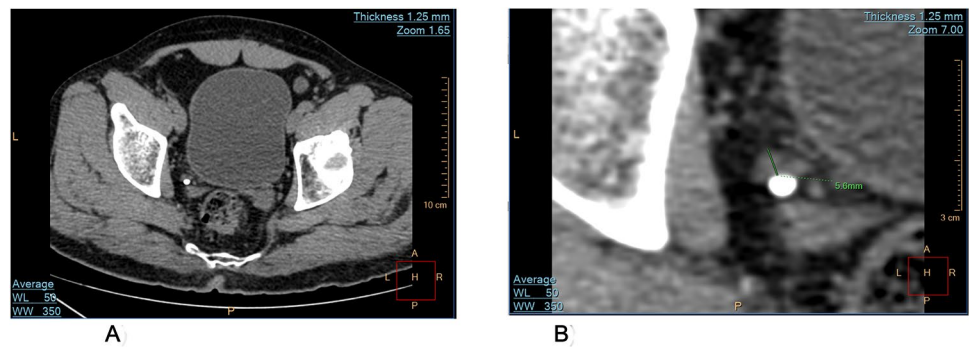


Fig. 1 Ureteral wall thickness as measured in axial cuts of NCCT. **a** A detection of right lower ureteric stone in the axial cuts of NCCT. **b** Fixed (7×) magnification is used to facilitate accurate demarcation of ureteral borders with soft-tissue radiodensity (width, 350; level, 50)



(SD), and range values. Independent *t* test was used for comparing quantitative variables between groups. Qualitative data were expressed as frequencies (*n*) and percentages (%). Chi-square and Fisher's exact tests were used to test association between qualitative variables. *p* value ≤ 0.05 was considered significant. Backward multivariate logistic regression analysis was performed for finding the predictors of treatment failure. Variables found to be significant in univariate analysis ($p < 0.1$) were included in the multivariate analysis model.

Results

We included 212 cases in the study. About 53% of cases had grade 1 hydronephrosis. The stone expulsion rate was 59.4%. There were 2 groups; 126 patients in the responder group and 86 patients in the non-responder group. The demographic data, NCCT findings, and stone expulsion rate are summarized in Table 1.

As seen in the demographic data, there was no significant difference in patient characteristics between responder and non-responder groups with regards to age or BMI. However, females had a significantly higher success rate compared to males (Table 1).

There was a significant difference between the responder and non-responder groups in relation to NCCT parameters such as stones' density, size, PUD, and UWT, with higher values in the non-responder group. Also, cases with lower hydronephrosis grade had higher success rates. On the other hand, there was no significant difference in stone laterality (Table 1).

Backward logistic regression was performed to predict failure. After including all significant variables ($p < 0.1$) in the univariate analysis, it was found that UWT and hydronephrosis grade were the independent factors affecting the passage of stone. Cases with higher UWT are more likely to fail (adjusted odds ratio = 7.08, CI = 3.68–13.6). It is a similar case with those scoring a higher hydronephrosis grade (adjusted odds ratio = 49.8, CI = 12.44–199.5).

Based on ROC analysis, the UWT could predict failure of stone passage at a cut-off level ≥ 3.75 , with 86% and 87.3% sensitivity and specificity, respectively.

Discussion

Although there is a debate on the value of MET in management of lower ureteric stone, MET in the guide line is recommended for the treatment of patients with uncomplicated distal ureteral stones ≤ 10 mm [10]. However, even small stones can get impacted. Therefore, controversy around who will most likely benefit from MET or who will require surgical intervention remains in the management of ureteral stones. Conservative management is a simpler and more cost-effective treatment than active stone removal [11]. However, conservative management is not free of stone-related complications (SRCs) such as recurrent pain, urosepsis, deterioration of renal function, and stone impaction [3]. Therefore, many efforts have been made to identify predictive factors for estimating SP in the clinical setting.

In recent studies, some possible and accurate predictors were determined that affect the success of SWL and URSL [12, 13]. These predictors were stone diameter, stone volume, HU, Hounsfield density of ureteral stones, and the grade of hydronephrosis. However, the effects of these factors on MET are not known. Therefore, more studies are needed to evaluate the value of these parameters in predicting the success of MET.

Stone impaction causes distinct pathological insults to the ureter. It is associated with inflammatory reactions which end up with ureteral edema, hypertrophy, and fibrosis that increases stone adhesion to the ureteral wall [6]. This inflammatory change leads to increase of UWT [1].

Recent studies have focused on the value of UWT in the management of ureteral stones. Sarica et al. [8], Özbir et al. [14], and Elibol et al. [15] concluded that UWT can be used as a sensitive predictor of stone impaction. Also, Yoshida et al. [9] reported that UWT is a reliable factor for predicting impacted stones and surgical outcomes post-URS.

Table 1 Demographic data and stone characters of all patients "responder and non-responder"

	Mean	± SD	Minimum	maximum	
Age (year)	42.14	14.73	19.00	73.00	
BMI (kg/m ²)	26.69	3.90	18.00	33.00	
Sex					
Male (<i>n</i> %)	118 (55.7%)				
Female (<i>n</i> %)	94(44.3)				
Side					
Right (<i>n</i> %)	114(53.7%)				
Left (<i>n</i> %)	98 (46.3%)				
Density (HU)	852.01	260.02	65.00	1320.00	
Size (mm)	6.74	1.51	5.00	10.00	
PUD (mm)	6.73	2.75	2.50	15.70	
UWT (mm)	3.72	1.83	0.30	8.10	
Hydronephrosis grade					
None (<i>n</i> %)	22 (10.4%)				
Grade I (<i>n</i> %)	112(52.8%)				
Grade II (<i>n</i> %)	78 (36.8%)				
	Responder		Non-responder		<i>p</i>
	Mean	± SD	Mean	± SD	
Age	41.94	13.45	42.44	16.50	0.814
BMI	26.43	3.34	27.07	4.59	0.240
Sex					
Male (<i>n</i> %)	62	52.5%	56	47.5%	0.022
Female (<i>n</i> %)	64	68.1%	30	31.9%	
Density	822.16	261.94	895.76	252.33	0.043
Size	6.19	1.35	7.54	1.39	0.001
PUD	5.19	1.36	9.00	2.70	0.001
UWT	2.77	1.00	5.11	1.88	0.001
Side					
Right	74	64.9%	40	35.1%	0.08
Left	52	53.1%	46	46.9%	
Hydronephrosis grade					
None	22	95.7%	1	4.3%	0.001
1	84	75.7%	27	24.3%	
2	20	25.6%	58	74.4%	

There are limited data on the use of UWT as a crucial predictor for ureteral stones that are treated using MET or spontaneous passage [1, 5, 16]. They noted that MET non-responders had significantly higher UWT than responders. This was also reported in our study where the UWT was a significant factor in predicting stone passage using MET.

In our study, the UWT cut-off level that predicted failure of stone passage was ≥ 3.75 mm. Yoshida et al. [1] reported the cut-off level of UWT, which predicted the 4 week SP, was 2.71 mm. Also, Yoshida et al. [9] reported that the optimal cut-off value for UWT for stone impaction, poor endoscopic findings, and adverse surgical outcomes in patients undergoing URSL was 3.49 mm.

Stone size and location are the most commonly studied predictive parameters for stone passage [17, 18]. Stone passage is higher in smaller and more distal stones in the ureter [17]. Larger stones have a low possibility of spontaneous passage [10, 19]. This is in agreement with the results of Sahin et al. [5] who reported that there was a significant relation between stone expulsion rates after MET and stone size and location ($p < 0.05$). Also, Yoshida et al. [1] found that the stone site and stone size ($p < 0.001$) were independent variables for predicting SP and stone size had a significantly higher predictive accuracy than stone location.

In our study where the MET responders had a highly significant lower stone size, after logistic regression that stone

size is not highly significant predictor of stone passage. This is in agreement with Celik et al. [20] who reported that stone diameter and stone volume were significantly lower in the successful group for distal stones ($p < 0.05$); after logistic regression analysis, none of stone diameter or stone volume was found to have significant effect. Also, Timothy et al. using univariate analysis found that stone size and volume to be predictive values of impacted stones. However, with the multivariate analysis, they were not a predictive value of stone impaction [21].

Regarding the degree of hydronephrosis, the MET responders had a highly significant lower degree of hydronephrosis even after logistic regression. This statistically significant difference is in agreement with the results of Sahin et al. [5] who reported that there was a significant relation between stone expulsion rates after MET and PUD and the degree of hydronephrosis ($p < 0.05$). Also, Özbir et al. [14] reported that the degree of hydronephrosis was a sensitive predictor of stone impaction. On the other hand, Yoshida et al. found that using univariate analysis, patients who passed a stone had a significantly lesser grade of hydronephrosis. When using multivariate analysis, the degree of hydronephrosis was not an independent variable for predicting SP [1]. At the same time, Celik et al. reported that the degree of hydronephrosis was significantly lower in the successful group for distal stones ($p < 0.05$). When considering the logistic regression analysis, hydronephrosis were found to have no significant effect [20].

Moreover, Timothy et al. on univariate analysis found hydronephrosis to be a predictive value of impacted stones. However, on multivariate analysis, hydronephrosis was not a predictive value of stone impaction [21].

In our study, females had significantly higher stone-free rates. This is also reported by Özbir et al. [14] as they found that males were more than females associated with stone impaction. On the other hand, Legemate et al. [19] found that females were more associated with higher rates of stone impaction. We believe that hormonal factors may be forming this causal relationship between gender and the success of MET. However, further studies are needed to explain this finding.

In our study, we found that stones with low density are more successfully expelled than those of high density and this difference was significant. However, after logistic regression was performed, HU did not have a significant predictive value in stone passage. This is in agreement with Celik et al., who reported that HU was significantly lower in the successful group for distal stones ($p < 0.05$). However, on considering the logistic regression analysis, HU was found to have no significant effect [20]. Furthermore, Erturhan et al. and Hada et al. demonstrated that stones with low HU pass easier through the ureter than those of high HU, but that was not significant. Therefore,

we can conclude that HU does not have any effect on SP [22, 23]. Sahin et al. [5] and Balci et al. [24] have confirmed this by reporting that HU is not a predictive parameter for stone expulsion, while Seitz et al. [6] have reported that stones of high density pass through the ureter slowly and with difficulty.

One of the difficulties encountered during measurement was how to measure the UWT exactly as fine tune of mm was difficult. First, fixed (7×) magnification was used to facilitate accurate demarcation of ureteral borders. More magnification could result in aliasing artifacts and makes the ureteric border little bit indistinct. Second, care was taken not to include the retroperitoneal fat or calculus in the region of interest. Finally, we must include the peri-ureteric edema and differentiate it from the adjacent normal retroperitoneal fat. The peri-ureteric edema usually appeared as haziness of peri-ureteric fat planes and could be included in UWT using the pre-defined soft-tissue window and fixed (7×) magnification. Therefore, (7×) magnification and soft-tissue window parameters were used as standardized method for assessing the UWT. Yoshida et al. [9] and Özbir et al. [14] had used the same technique regarding the pre-defined soft-tissue window and manual measurement of greatest soft-tissue thickness (ureteral wall $\pm$ peri-ureteral edema) around the circumference of the stone. Trimothy et al. [21] had used maximal (8×) magnification to facilitate accurate demarcation of ureteral borders.

Our study's main limitation has mainly to do with the measuring technique used for the UTW, which was performed manually by the radiologist; automated software is needed. More multicenter studies on larger scale of patients are needed to establish a nomogram for predicting of MET success. However, we believe that our findings will be contributive enough to the ongoing research about this critical subject.

Conclusion

UWT and degree of hydronephrosis may be predictive of stone passage. Use of these parameters may enable us to avoid unnecessary use of MET and distinguish patients in need for prompt surgical intervention.

Author contributions AT: project development, data management, and manuscript writing and editing; MS: project development and data management; EH: project development and data management.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

The research involving human participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. And the study was approved by hospital ethical committee.

Informed consent Informed consent was obtained from all individual participants in the study.

References

- Yoshida T, Inoue T, Taguchi M, Omura N, Kinoshita H, Matsuda T (2019) Ureteral wall thickness as a significant factor in predicting spontaneous passage of ureteral stones of ≤ 10 mm: a preliminary report. *World J Urol* 37:913
- Ahmed AF, Al-Sayed AY (2010) Tamsulosin versus Alfuzosin in the treatment of patients with distal ureteral stones: prospective, randomized, comparative study. *Korean J Urol* 51:193–197
- Assimos D, Krambeck A, Miller NL et al (2016) Surgical management of stones: American Urological Association/Endourological Society Guideline, PART II. *J Urol* 196:1161–1169
- Kobayashi T, Nishizawa K, Watanabe J, Ogura K (2003) Clinical characteristics of ureteral calculi detected by nonenhanced computerized tomography after unclear results of plain radiography and ultrasonography. *J Urol* 170(799):802
- Sahin C, Eryildirim B, Kafkasli A et al (2015) Predictive parameters for medical expulsive therapy in ureteral stones: a critical evaluation. *Urolithiasis* 43:271
- Seitz C, Tanovic E, Kikic Z, Fajkovic H (2007) Impact of stone size, location, composition, impaction, and hydronephrosis on the efficacy of holmium:YAG-laser ureterolithotripsy. *Eur Urol* 52:1751–1759
- Chaussy CG, Fuchs GJ (1989) Current state and future developments of noninvasive treatment of human urinary stones with extracorporeal shock wave lithotripsy. *J Urol* 141:782–789
- Sarica K, Kafkasli A, Yazici Ö, Sabuncu K, Cetinel C, Narter F (2015) Ureteral wall thickness at the impacted ureteral stone site: a critical predictor for success rates after SWL. *Urolithiasis* 43:83–88
- Yoshida T, Inoue T, Omura N et al (2017) Ureteral wall thickness as a preoperative indicator of impacted stones in patients with ureteral stones undergoing ureteroscopic lithotripsy. *Urology* 106:45–49
- Turk C, Knoll T, Seitz C, Skolarikos A, Chapple C, McClinton S (2017) European Association of Urology, Medical Expulsive Therapy for Ureterolithiasis: the EAU Recommendations in 2016. *Eur Urol* 71:504–507
- Bensalah K, Pearle M, Lotan Y (2008) Cost-effectiveness of medical expulsive therapy using alpha-blockers for the treatment of distal ureteral stones. *Eur Urol* 53:411
- Ito H, Kawahara T, Terao H, Ogawa T, Yao M, Kubota Y et al (2012) Predictive value of attenuation coefficients measured as Hounsfield units on noncontrast computed tomography during flexible ureteroscopy with holmium laser lithotripsy: a single-center experience. *J Endourol* 26:1125
- Celik S, Bozkurt O, Kaya FG, Egriboyun S, Demir O, Secil M et al (2015) Evaluation of computed tomography findings for success prediction after extracorporeal shock wave lithotripsy for urinary tract stone disease. *Int Urol Nephrol* 47:69–73
- Özbir S, Can O, Atalay HA, Canat HL, Çakır S, Ötünçtemur A (2019) Formula for predicting the impact of ureteral stones. *Urolithiasis*. <https://doi.org/10.1007/s00240-019-01152-y>
- Elibol O, Safak KY, Buz A, Eryildirim B, Erdem K, Sarica K (2017) Radiological noninvasive assessment of ureteral stone impaction into the ureteric wall: a critical evaluation with objective radiological parameters. *Investig Clin Urol* 58(5):339–345
- Tuerxun A, Batuer A, Erturhan S, Eryildirim B, Camur E, Sarica K (2017) Impaction and prediction: does ureteral wall thickness affect the success of medical expulsive therapy in pediatric ureteral stones? *Urol Int* 98:436–441
- Coll DM, Varanelli MJ, Smith RC (2002) Relationship of spontaneous passage of ureteral calculi to stone size and location as revealed by unenhanced helical CT. *AJR Am J Roentgenol* 178:101–103
- Lee SR, Jeon HG, Park DS, Choi YD (2012) Longitudinal stone diameter on coronal reconstruction of computed tomography as a predictor of ureteral stone expulsion in medical expulsive therapy. *Urology* 80:784–789
- Legemate JD, Wijnstok NJ, Matsuda T et al (2017) Characteristics and outcomes of ureteroscopic treatment in 2650 patients with impacted ureteral stones. *World J Urol* 35(10):1497–1506
- Celik S, Akdeniz F, Afsar-Yildirim M, Bozkurt O, Gursay-Bulut M, Mehmet LH, Omer D (2017) Computed tomography findings predicting the success of silodosin for medical expulsive therapy of ureteral stones. *Kaohsiung J Med Sci* 33:290–294
- Tran TY, Bamberger JN, Blum KA, Parkhomenko E, Thai J, Chandhoke RA, Gupta M (2019) Predicting the impacted ureteral stone with computed tomography. *Urology* 130:43–47
- Erturhan S, Bayrak O, Mete A, Seckiner I, Urgun G, Sarica K (2013) Can the Hounsfield unit predict the success of medically expulsive therapy? *Can Urol Assoc J* 7(11–12):E677–E680
- Hada A, Yadav SS, Tomar V, Priyadarshi S, Agarwal N, Gulani A (2018) Assessment of factors affecting the spontaneous passage of lower ureteric calculus on the basis of lower ureteric calculus diameter, density, and plasma C-reactive protein level. *Urol Ann* 10(3):302–307
- Balci M, Tuncel A, Aydin O, Aslan Y, Guzel O, Toprak U et al (2014) Tamsulosin versus nifedipin in medical expulsive therapy for distal ureteral stones and the predictive value of Hounsfield unit in stone expulsion. *Ren Fail* 36:1541

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Terms and Conditions

Springer Nature journal content, brought to you courtesy of Springer Nature Customer Service Center GmbH (“Springer Nature”).

Springer Nature supports a reasonable amount of sharing of research papers by authors, subscribers and authorised users (“Users”), for small-scale personal, non-commercial use provided that all copyright, trade and service marks and other proprietary notices are maintained. By accessing, sharing, receiving or otherwise using the Springer Nature journal content you agree to these terms of use (“Terms”). For these purposes, Springer Nature considers academic use (by researchers and students) to be non-commercial.

These Terms are supplementary and will apply in addition to any applicable website terms and conditions, a relevant site licence or a personal subscription. These Terms will prevail over any conflict or ambiguity with regards to the relevant terms, a site licence or a personal subscription (to the extent of the conflict or ambiguity only). For Creative Commons-licensed articles, the terms of the Creative Commons license used will apply.

We collect and use personal data to provide access to the Springer Nature journal content. We may also use these personal data internally within ResearchGate and Springer Nature and as agreed share it, in an anonymised way, for purposes of tracking, analysis and reporting. We will not otherwise disclose your personal data outside the ResearchGate or the Springer Nature group of companies unless we have your permission as detailed in the Privacy Policy.

While Users may use the Springer Nature journal content for small scale, personal non-commercial use, it is important to note that Users may not:

1. use such content for the purpose of providing other users with access on a regular or large scale basis or as a means to circumvent access control;
2. use such content where to do so would be considered a criminal or statutory offence in any jurisdiction, or gives rise to civil liability, or is otherwise unlawful;
3. falsely or misleadingly imply or suggest endorsement, approval, sponsorship, or association unless explicitly agreed to by Springer Nature in writing;
4. use bots or other automated methods to access the content or redirect messages
5. override any security feature or exclusionary protocol; or
6. share the content in order to create substitute for Springer Nature products or services or a systematic database of Springer Nature journal content.

In line with the restriction against commercial use, Springer Nature does not permit the creation of a product or service that creates revenue, royalties, rent or income from our content or its inclusion as part of a paid for service or for other commercial gain. Springer Nature journal content cannot be used for inter-library loans and librarians may not upload Springer Nature journal content on a large scale into their, or any other, institutional repository.

These terms of use are reviewed regularly and may be amended at any time. Springer Nature is not obligated to publish any information or content on this website and may remove it or features or functionality at our sole discretion, at any time with or without notice. Springer Nature may revoke this licence to you at any time and remove access to any copies of the Springer Nature journal content which have been saved.

To the fullest extent permitted by law, Springer Nature makes no warranties, representations or guarantees to Users, either express or implied with respect to the Springer nature journal content and all parties disclaim and waive any implied warranties or warranties imposed by law, including merchantability or fitness for any particular purpose.

Please note that these rights do not automatically extend to content, data or other material published by Springer Nature that may be licensed from third parties.

If you would like to use or distribute our Springer Nature journal content to a wider audience or on a regular basis or in any other manner not expressly permitted by these Terms, please contact Springer Nature at

onlineservice@springernature.com