## 10 – ORIGINAL ARTICLE SYSTEMATIC REVIEWS AND META-ANALYSIS

# A meta-analysis of the efficacy of ureteroscopic lithotripsy and extracorporeal shock wave lithotripsy on ureteral calculi

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#### **ABSTRACT**

**PURPOSE:** To re-evaluated the clinic efficacy of ureteroscopic lithotripsy (URS) and extracorporeal shock wave lithotripsy (ESWL) on ureteral calculi with Cochrane systematic reviews in this paper.

**METHODS:** We searched clinical randomized controlled trials and prospective controlled trials in databases such as Cochrane library, Medline, Springer, Elsevier Science Direct, PubMed. Pooled estimate of risk ratios (RRs), standard mean difference (SMD) with 95% confidence intervals (CIs) were used as measure of effect sizes. Summary effect estimates were also stratified by sample size, study design and study region. The overall effect sizes were derived using a random-effects model or fixed-effects model when appreciated, and meta-analysis were conducted with software RewMan 5.0.

**RESULTS:** The meta-analysis suggested that there were significant differences of post-treatment stone free rate, repeat treatment rate, patients' satisfaction, incidence of postoperative complications, operation time and hospital stays between ESWL treatment cases and URS treatment cases. But in the sample sizes analysis, there were no significant differences of the post-treatment stone free rate and repeat treatment rate when the sample sizes were less than 100.

**CONCLUSIONS:** Compared to the ureteroscopic lithotripsy treatment, extracorporeal shock wave lithotripsy treatment provided a significantly lower post-treatment stone free rate, but it also obviously brought out less postoperative complications, shorter operation time and hospital stays.

Key words: Lithotripsy (MeSH). Ureteroscoy (MeSH). Ureteral Calculi. Meta-Analysis.

#### Introduction

The presence of calculi in the urinary system is defined as urolithiasis, which represents the symptomatic manifestation of various metabolic disturbances, caused by a variety of pathological factors and their interaction. Urolithiasis is a common and frequently-occurring disease with increased morbidity and high recurrence rate, including renal calculi, ureteral calculi, cystolith and urethral calculi, among which ureteral calculi is the most commonly one. So far, ureteroscopic lithotripsy (URS) and extracorporeal shock wave lithotripsy (ESWL) are principle therapies in ureteral calculi treatment with satisfactory curative effect in the vast majority of cases, and both have its own advantages and disadvantages.

ESWL, dates back to 1980s, is a clinically proved method of totally noninvasive, with low cost, few complications and no or shorter hospitalization<sup>4-6</sup>. URS is more invasive and done under general anaesthesia, but significantly better in terms of operative time, fluoroscopy time and time to achieve a stone-free state<sup>6-8</sup>. URS is also better in broking hard stones and the ureter opening is simultaneously dilated by the scope to facilitate subsequent stone passage. In Middela *et al.*<sup>9</sup> study, ESWL was demonstrated an effective and minimally invasive method for treating ureteral stones. While Hong and Park demonstrated that despite the liberal use of ESWL, ureteroscopic lithotripsy was still the preferred treatment modality for managing ureter stones at many hospitals and achieves an immediate stone-free state in a high percent of patients<sup>10</sup>. So it is still controversial which treatment is clinical preferred.

Recently, plenty researches compared URS and ESWL in ureteral calculi therapy, but obtained various results due to the differences in research design, recruit and exclusion criteria, measurement methods and so on. In this paper, we collected clinical prospective studies on URS and ESWL, and applied meta-analysis to evaluate the clinic efficacy of URS and ESWL comprehensively.

## Methods

Source of material

We retrieved literatures in a systematic way from the Cochrane library, Medline, Springer, Elsevier Science Direct, PubMed and EMbase concerning URS and ESWL treating ureteral calculi with the retrieval deadline of December 2012. The search terms included "ureteral stones", "ureteral calculi", "extracorporeal shock wave lithotripsy" and "ureteroscopy and randomized controlled trials". In addition, a manual search of

citations from relevant original studies and review articles was performed for any additional studies.

## Inclusion and exclusion criteria

Studies were included in the meta-analysis if they met the following criteria: (1) research papers publicly published abroad; (2) research objects were adult patients with ureteral diseases definitely diagnosed by imaging; (3) the study design were clinical prospective study; (4) studies should include treatments of ureteroscopic lithotripsy (URS) and extracorporeal shock wave lithotripsy (ESWL); (5) data should be integrity, and the number of cases in different treatment groups as well as cases finished the trials should be explicit; (6) observation index should include authors, published journals and time, patients quantity and their operation time, hospital stays, rate of stone free post treatment, rate of repeat treatment and postoperative complications. Besides, references would be excluded when appeared the following conditions: 1) article was non-English literature; 2) paper was re-publication or the literature was used with same population data; 3) article was non-original literature such as review, letters and comments.

#### Data extraction and literature evaluation

The data were independently extracted and collected in unified forms from the primary studies by two reviewers. The data items included study details such as sample size, cases loss to follow-up and/or withdraw and research index/data. Disagreement was defused by discussion or the third researchers.

Jadad scale<sup>11</sup> was applied to assess the methodological quality of recruited clinical trials based on the extracted information such as study design, patients, and the clinical outcomes. The evaluations were also performed by two assessors independently. The recruited studies were defined with high quality when their Jadad score were  $\geq 3$ .

## Statistical analysis

Meta-analysis was carried out by RevMan 5.0 provided by the Cochrane Collaboration. The point estimates of RR, SMD and their 95% CIs were calculated as effect sizes. We assessed the heterogeneity by testing Cochran's Q-statistic<sup>12</sup> and using  $I^2 = 100\% \times (Q-df)/Q^{13}$ . A significant Q-statistic ( $I^2 > 50\%$ ) indicated heterogeneity were existed between studies, and then the random effect model should be used for meta-analysis. Otherwise, heterogeneity is not significant and the fixed effect model

was applied. We further conducted subgroup analysis according to sample size (<100/≥100), study design (RCT/Non-randomized) and study region (Europe and America / Asia and Africa) to investigate the impacts of study characteristics on our outcomes.

#### Results

## Eligible studies and the characteristics

According to the above retrieval method, 829 potentially relevant trials in total were yielded. After screening their titles, abstracts and full publication reviewing, we removed reviews, case reports and retrospective studies. Finally, a total 13 English papers were eligible and recruited in our analysis<sup>14-26</sup>, whose general characteristics were shown in Table 1. The included studies were published between 1999 and 2013. A total of 2005 patients (998 ESWL treatment cases and 1007 URS treatment cases) were considered in the meta-analysis. The studies' sample size was between 13 and 210. In addition, there were 4 high quality studies with Jadad Score 3 and 9 studies with Jadad Score 2.

**TABLE 1 -** General characteristics of the 13 eligible literatures/ trials involved.

trais involved.				
Study and Publication	Country/Region	sample size	Follow- up Time	Jadad Score
year		(ESWL/		
		URS)		
Hendrikx, 1999	The Netherlands	69/87	3 months	3
Peschel, 1999	Australian	40/40	6 weeks	2
Pearle, 2001	The U.S.A	32/32	3 months	3
Zeng, 2002	China	210/180	4 weeks	2
Lee, 2006	Taiwan	22/20	NA	3
Salem, 2009	Egypt	100/100	3 months	2
Verze, 2010	Italy	137/136	3 months	2
Lopes, 2012	Brazil	13/13	2 months	2
Islam, 2012	Pakistan	68/68	3 months	3
Hosking, 2003	Canada	110/172	3 months	2
Honeck, 2006	Germany	62/62	NA	2
Khalil, 2013	Kuwait	37/45	3 months	2
Strohmaier, 1999	Germany	97/49	NA	2

NA: not available

## Meta-analysis of the stone free rate

All the 13 papers<sup>14-26</sup> reported the differences of stone free rate of patients after the treatment of ESWL and URS. The heterogeneity results (P<0.00001, *I*<sup>2</sup>=83%) indicated significant heterogeneities were existed between the studies, so we used the random effect model to evaluate the pooled estimates. The pooled RR (95% CI) was 0.82 (0.74-0.90) and the p-value of the test for overall effect was less than 0.0001 which demonstrated there was a significant 18% decrease of stone free rate of patients treated with ESWL compared to the URS surgeries (Figure 1).

	ESW	L	URS			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Hendrikx 1999	35	69	79	87	6.5%	0.56 [0.44, 0.71]	
Honeck 2006	52	62	61	62	9.6%	0.85 [0.76, 0.96]	-
Hosking 2003	72	110	163	172	9.0%	0.69 [0.60, 0.79]	
Islam 2012	50	68	64	68	8.6%	0.78 [0.67, 0.91]	
Khalil 2013	29	37	37	45	7.0%	0.95 [0.77, 1.18]	<del>-</del>
Lee 2006	7	22	7	20	1.1%	0.91 [0.39, 2.14]	<del></del>
Lopes 2012	5	14	10	16	1.3%	0.57 [0.26, 1.27]	<del></del>
Pearle 2001	29	32	29	32	8.5%	1.00 [0.85, 1.17]	+
Peschel 1999	36	40	40	40	9.6%	0.90 [0.81, 1.01]	<del>-  </del>
Salem 2009	71	100	96	100	9.2%	0.74 [0.65, 0.84]	-
Strohmaier 1999	68	97	46	49	8.8%	0.75 [0.64, 0.87]	
Verze 2010	127	137	129	136	10.6%	0.98 [0.92, 1.04]	†
Zeng 2002	164	210	168	180	10.3%	0.84 [0.77, 0.91]	*
Total (95% CI)		998		1007	100.0%	0.82 [0.74, 0.90]	•
Total events	745	-00	929			5.52 [617-4, 616-6]	-
Heterogeneity: Tau <sup>2</sup> =		P = 70 1		2 (P < 1	000011	I <sup>2</sup> = 83%	+ + + + + + + + + + + + + + + + + + + +
Test for overall effect:				- ( (	3.00001),	00%	0.2 0.5 1 2 5
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**FIGURE 1** - Meta-analysis forest plots of stone free rate associated with the ureteroscopic lithotripsy (URS) vs. extracorporeal shock wave lithotripsy (ESWL).

## Meta-analysis of the repeat treatment rate

A total of 10 papers<sup>14-21,24,26</sup> were analyzed with the repeat treatment rate of patients after the two different therapeutic methods. There was significant heterogeneities (P<0.00001, *I*<sup>2</sup>=85%) between the recruited studies and random effects model was applied for the analysis. The overall estimates of RR was 3.46 (95%CI: 1.50-7.97) and the test p-value for overall effect was 0.004 (Figure 2). It pointed out that there were significant differences of repeat treatment rate between the ESWL and URS.

	ESW	L	URS	;		Risk Ratio	Risk R	atio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Randor	n, 95% CI
Hendrikx 1999	31	69	8	87	14.1%	4.89 [2.40, 9.94]		
Islam 2012	5	68	13	65	12.9%	0.37 [0.14, 0.97]	-	
Khalil 2013	16	37	1	45	8.4%	19.46 [2.71, 139.94]		
Lee 2006	7	22	8	20	13.6%	0.80 [0.35, 1.79]		-
Lopes 2012	12	14	2	16	11.3%	6.86 [1.84, 25.51]		
Pearle 2001	0	32	0	32		Not estimable		
Peschel 1999	0	40	0	40		Not estimable		
Salem 2009	29	100	4	100	12.8%	7.25 [2.65, 19.87]		
Verze 2010	57	137	10	136	14.4%	5.66 [3.02, 10.61]		-
Zeng 2002	25	210	4	180	12.6%	5.36 [1.90, 15.10]		
Total (95% CI)		729		721	100.0%	3.46 [1.50, 7.97]		•
Total events	182		50					
Heterogeneity: Tau <sup>2</sup> =	: 1.16: Chi	$i^2 = 43$ .	46. df = 7	(P < 0.	00001): P	<sup>2</sup> = 84%	L	<del> </del>
Test for overall effect:					//		0.01 0.1 1 Favours ESWL I	10 100 Favours URS

**FIGURE 2** - Meta-analysis forest plots of repeat treatment rate associated with the ureteroscopic lithotripsy (URS) vs. extracorporeal shock wave lithotripsy (ESWL).

## Meta-analysis of the patients' satisfaction

There were only two papers<sup>14,17</sup> studied the patients' satisfaction after treatment with ESWL and URS. Fixed effects model were chose for the meta-analysis as the no-significant heterogeneity (P=0.85, I²=0.0%). In Figure 3, the total estimates (P=0.02, RR=0.87, 95%CI: 0.78-0.98) showed that patients' satisfaction in URS group was higher than ESWL group significantly.

	ESW	L	URS	5		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	_		
Lopes 2012	11	14	16	16	27.6%	0.79 [0.59, 1.06]	<del></del>			
Peschel 1999	35	40	40	40	72.4%	0.88 [0.77, 0.99]	-	1		
Total (95% CI)		54		56	100.0%	0.85 [0.76, 0.96]	•			
Total events	46		56					I		
Heterogeneity: Chi² = 0.45, df = 1 (P = 0.50); i² = 0%										
Test for overall effect	Z= 2.60	(P = 0.0	109)				0.5 0.7 1 1.5 2 Favours ESWL Favours URS	1		

**FIGURE 3** - Meta-analysis forest plots of patients' satisfaction in ureteroscopic lithotripsy (URS) treated group and extracorporeal shock wave lithotripsy (ESWL) treated group.

## Meta-analysis of the postoperative complications

A total of 10 papers<sup>14-21,24,26</sup> were analyzed with patients' postoperative complications. The heterogeneity results (P<0.08, P=43%) indicated non-significant heterogeneities were existed between the studies, so fixed effects model were applied to evaluate the pooled estimates. The total RR of 0.63 (95%CI: 0.48-0.83, P=0.40) described that ESWL had a significant 37% reduce of postoperative complications compared to URS in the ureteral calculi treatment (Figure 4).

	ESW	L	URS	;		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	_
Hendrikx 1999	14	69	30	87	23.8%	0.59 [0.34, 1.02]		
Islam 2012	5	68	6	68	5.4%	0.83 [0.27, 2.60]	<del></del>	
Khalil 2013	9	37	7	45	5.7%	1.56 [0.64, 3.80]	+-	tı
Lee 2006	2	22	18	20	16.9%	0.10 [0.03, 0.38]		u
Lopes 2012	1	14	3	16	2.5%	0.38 [0.04, 3.26]		G.
Pearle 2001	3	32	8	32	7.2%	0.38 [0.11, 1.29]	<del></del>	S
Peschel 1999	0	40	0	40		Not estimable		2
Salem 2009	2	100	4	100	3.6%	0.50 [0.09, 2.67]	<del></del>	3
Verze 2010	21	137	26	136	23.4%	0.80 [0.47, 1.35]	<del></del>	
Zeng 2002	12	210	12	180	11.6%	0.86 [0.39, 1.86]	<del>-</del>	W
							•	_
Total (95% CI)		729		724	100.0%	0.63 [0.48, 0.83]	▼	9
Total events	69		114					
Heterogeneity: Chi <sup>2</sup> =				= 43%			0.05 0.2 1 5 20	- 0
Test for overall effect:	Z = 3.30 (	P = 0.0	1010)				Favours ESWL Favours URS	
							Taronio Lorre	+1

**FIGURE 4** - Meta-analysis forest plots of postoperative complications in ureteroscopic lithotripsy (URS) treated group and extracorporeal shock wave lithotripsy (ESWL) treated group.

## Meta-analysis of the operation time

There were three papers<sup>17,18,20</sup> analyzed the operation time of the two different therapeutic methods. Random effects model were chose due to the poor heterogeneity (P=0.04, *I*<sup>2</sup>=70%). The total estimates (P=0.002, SMD=-1.12, 95%CI: -1.81- -0.43) demonstrated that the operation time in URS group was significant longer than that in the ESWL group (Figure 5).

	Study or Subgroup	E Mean	SWL SD	Total	Mean	URS SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% CI
	Lee 2006	43.2	5	22	109	50.1	20	31.2%	-1.86 [-2.60, -1.12]	-
	Lopes 2012	44.5	10.3	14	72.8	42	16	30.6%	-0.87 [-1.63, -0.12]	<del></del>
,	Pearle 2001	71.8	22.4	32	96.6	43.2	32	38.3%	-0.71 [-1.22, -0.21]	-
	Total (95% CI)			68			68	100.0%	-1.12 [-1.81, -0.43]	•
Heterogeneity: Tau² = 0.26; Chi² = 6.56, df = 2 (P = 0.04); l² = 70%									-2 -1 0 1 2	
	Test for overall effect:	Z = 3.17	(P = 0	).002)						Favours ESWI Favours URS

**FIGURE 5** - Meta-analysis forest plots of operation time in ureteroscopic lithotripsy (URS) treated group and extracorporeal shock wave lithotripsy (ESWL) treated group.

## Meta-analysis of the hospital stays

There were three papers<sup>17,18,20</sup> studied the hospital stays of patients with the treatment of ESWL and URS. The heterogeneity results (P=0.0001, *P*=89%) indicated significant heterogeneities were existed between the studies, so random fixed effects model were applied to evaluate the pooled estimates. The pooled estimates (P=0.004, SMD=-1.71, 95%CI: -2.88- -0.55) demonstrated that the hospital stays in URS group was also significant longer than that in the ESWL group (Figure 6).

	ESWL URS				URS Std. Mean Difference				Std. Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
Hendrikx 1999	2.2	2.6	69	4.4	3.1	87	37.2%	-0.76 [-1.08, -0.43]	<b>=</b>		
Lee 2006	1.8	0.4	22	4.7	2	20	33.0%	-2.02 [-2.78, -1.26]	-		
Lopes 2012	1.9	1.2	14	27.8	13.4	16	29.9%	-2.56 [-3.56, -1.56]	-		
Total (95% CI) 105 123 100.0% -1.71 [-2.88, -0.55]									•		
Heterogeneity: Tau <sup>2</sup> =		4 -2 0 2 4									
Test for overall effect:	Z = 2.88	(P=	0.004)						Favours FSWI Favours URS		

**FIGURE 6** - Meta-analysis forest plots of hospital stays in ureteroscopic lithotripsy (URS) treated group and extracorporeal shock wave lithotripsy (ESWL) treated group.

## Subgroup analysis

The subgroup analysis of stone free rate and repeat treatment rate of ureteral calculi patients stratified by the sample size, study design and study region were showed in Tables 2 and 3, respectively. In the stratified analysis by the sample size, there were no significant difference of the stone free rate (RR=0.91; 95%CI: 0.82-1.02) and repeat treatment rate (RR=4.21; 95%CI: 0.50-35.60) of the patients treated with ESWL and URS when the sample size was smaller than 100. In addition, the outcomes of stone free rate stratified by the study design were RR=0.82 (95%CI: 0.73-0.93) and RR= 0.80 (95%CI: 0.70-0.91) of the RCT and non-randomized studies, respectively, while the repeat treatment rate of RCT and non-randomized studies were RR=2.96 (95%CI: 1.25-6.97) and RR=19.46 (2.71-139.94). Besides, the outcomes of subgroups stratified by the study region were RR=0.81 (95%CI: 0.69-0.94; Europe and America) and RR=0.81 (95%CI: 0.76-0.88; Asia and Africa) of the stone free rate, and repeat treatment rate were RR=5.46 (95%CI: 3.51-8.51; Europe and America) and RR=2.64 (95%CI: 0.66-10.54; Asia and Africa). The results indicated that the outcomes of the stone free rate and repeat treatment rate stratified by the study design and study region were consisted with the pooled estimates.

**TABLE 2** - Subgroup analyses of stone free rate of ureteral calculi patients treated with ESWL and URS.

Group	No. of	RR (95%CI)	Heterogenei	Significance		
	studies		P I <sup>2</sup> (	(%)	test (P)	
All studies	13	0.82	< 0.00001	83.0	< 0.0001	
		(0.74, 0.90)				
sample size						
<100	5	0.91	0.60	0.0	0.11	
		(0.82, 1.02)				
≥100	8	0.78	< 0.00001	89.0	< 0.0001	
		(0.69, 0.88)				
study design						
RCT	9	0.82	< 0.00001	85.0	0.002	
		(0.73, 0.93)				
Non-	4	0.80	0.03	68.0	0.0007	
randomized		(0.70, 0.91)				
study region						
Europe and	8	0.81	< 0.00001	90.0	0.005	
America		(0.69, 0.94)				
Asia and	5	0.81	0.30	17.0	< 0.0001	
Africa		(0.76, 0.88)				

**TABLE 3** - Subgroup analyses of repeat treatment rate of ureteral calculi patients treated with ESWL and URS.

Group	No. of	RR (95%CI)	Heterogeneity tes		Significance
	studies		P I <sup>2</sup>	(%)	test (P)
All studies	10	3.46 (1.50,7.97)	< 0.00001	84.0	0.004
sample size					
<100	5	4.21	0.0003	88.0	0.19
		(0.50, 35.60)			
≥100	5	3.36 (1.28,8.81)	< 0.00001	85.0	0.01
study design					
RCT	9	2.96 (1.25,6.97)	< 0.00001	85.0	0.01
Non-	1	19.46			
randomized		(2.71, 139.94)			
study region					
Europe and	5	5.46 (3.51,8.51)	0.89	0.0	< 0.00001
America					
Asia and	5	2.64	< 0.00001	88.0	0.17
Africa		(0.66, 10.54)			

#### Discussion

It is well known that ESWL and URS are the main techniques in treating ureteral calculi. But the choice of ESWL or URS for ureteric stone management is one of the most commonly debated controversies in endourology, which may be partly attributable to parallel technology advancement in both fields<sup>27</sup>. In order to provide evidences for choosing which technique is better for patients, we applied meta-analysis to comprehensively evaluate the efficacy of ESWL and URS in treating ureteral calculi. The present work included 13 recruited studies associated with the efficacy of ESWL and URS, which were representative and filtered from several countries and multi-centers. And our analysis demonstrated that URS was superior to ESWL on post-treatment stone free rate, repeat treatment rate and patients' satisfaction, while the incidence of postoperative complications, operation time and hospital stays of ESWL was obviously lower or shorter than URS.

Since URS is more invasive than ESWL, URS resulted in a remarkably higher stone-free rate and lower repeat treatment rate. Especially in large, distal stones the failure rate of ESWL was high<sup>25,28,29</sup>. Our analysis was in accordance with these studies. URS is also performed with longer operation time, hospital stays and more postoperative complications for its invasiveness. Besides, Bierkens *et al.*<sup>30</sup> reported on complications following URS with small caliber instruments were decreased. And some studies also showed that the complication rate of URS was low and comparable with ESWL when the surgeries were in the hands of an experienced urologist<sup>25,29,31</sup>. Meanwhile, researches supported ESWL as the treatment of choice for ureteral stones as there were less complications and no need for major anesthesia with ESWL<sup>32,33</sup>.

The observed high heterogeneity in the pooled metaanalysis and the subgroup analysis indicated that the sample size, study design and study region affected the heterogeneity little. As the results of stone free rate and repeat treatment rate were not significant difference between the ESWL and URS when sample size <100, so the sample size could have an effect on the total estimates even it affected the heterogeneity little.

Nevertheless, there were certain limitations in our meta-analysis. Firstly, the sample size of some eligible trails is small; whether the eligible studies applied the blind method is not known; and the position and/or the size of the stone which might influence the treatment outcome are also unclear. Secondly, there are inevitably different judgment standards on the study indexes since trails were launched in different countries and regions with different researchers. Thirdly, the follow-up time of the studies

differs, which might impact the outcomes. Therefore, further assessment with large sample sizes, clearly subgroup analyses (such as size and position of stones) and uniform follow-up information of postoperative complications should be carried out to evaluate the efficacy of ESWL and URS.

#### Conclusion

Extracorporeal shock wave lithotripsy performed with less postoperative complications, shorter operation time and hospital stays, and ureteroscopic lithotripsy provided better efficacy of higher post-treatment stone free rate, lower repeat treatment rate and higher patients' satisfaction on the ureteral calculi treatment.

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