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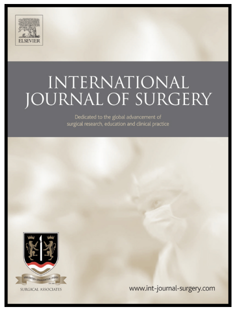

Optimal management of large proximal ureteral stones (>10mm): a systematic review and meta-analysis of 12 randomized controlled trials

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Optimal management of large proximal ureteral stones (>10mm): a systematic review and meta-analysis of 12 randomized controlled trials

Running title: Optimal management of large proximal ureteral stones

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Optimal management of large proximal ureteral stones (>10mm): a systematic review and meta-analysis of 12 randomized controlled trials

Key words:

Extracorporeal shockwave lithotripsy (ESWL); Large proximal ureteral stones (LPUS); Laparoscopic ureterolithotomy (LU); Percutaneous nephrolithotomy (PCNL); Systematic review and Meta-analysis; Ureteroscopic lithotripsy (URL)

Abbreviations:

AMSTAR=Assessing the methodological quality of systematic reviews; CI=confidence interval; ESWL=Extracorporeal shockwave lithotripsy; LE = level of evidence; LPUS=Large proximal ureteral stones; mPCNL=minimally invasive percutaneous nephrolithotomy; PCNL=standard percutaneous nephrolithotomy; PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-analysis; RCT=randomized control trial; RR=Risk ratio; SFR= stone-free rate; URL= transurethral ureteroscope lithotripsy; WMD= Weighted mean difference; PCNL=standard percutaneous nephrolithotomy;

Abstract

Objectives:

To develop an evidence base to guide clinicians treating adults with large proximal ureteral stones (LPUS) greater than 10mm.

Methods:

A systematic search of PubMed, EMBASE, and Cochrane Library was conducted to identify randomized controlled trials (RCT) concerning different LPUS management techniques including laparoscopic ureterolithotomy (LU), percutaneous nephrolithotomy (PCNL) and ureteroscopic lithotripsy (URL) up until March 2020. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement when searching and determining inclusion. All included articles were quality assessed and the data analyses were conducted with Review Manager (5.3).

Results:

12 RCTs involving 1416 patients met our eligibility criteria and were analyzed. Of these participants, 44.6% (n = 632) underwent URL, 25.5% (n = 361) PCNL, and 29.9% (n = 423) LU. Pooled analysis revealed that URL had a significantly lower stone-free rate (SFR) compared to PCNL and LU (both with $p<0.05$). URL had a significantly higher ureteral injury rate compared to LU (Relative risk (RR)=5.27, 95% confidence interval (CI) 1.52 to 18.22, p=0.009) and PCNL (RR=4.11, 95% CI 1.03 to 16.34, p=0.04). However, no significant differences were found between PCNL and LU in terms of SFR or overall complications, both with $p>0.05$. URL initially costs less than PCNL (Weighted mean difference (WMD) -597.35US$, 95% CI -823.10 to -371.60, $p<0.00001$), but being less effective creates greater demand for repeat or ancillary treatments compared to LU (RR 15.65, 95% CI 2.11–116.12, $p=0.007$) and PCNL (RR 8.86; 95% CI

3.19-24.60; $p<0.00001$).

Conclusions:

Both PCNL and LU appear more effective and safer than URL for LPUS; although, LU has higher risk of urine leakage and is more likely incur trauma which requires additional support. However, caution must be taken because this recommendation is based upon a very limited number of clinical studies，and even fewer comparing flexible ureteroscopic technologies. Further prospective real-world studies or RCTs comparing flexible URL, LU and PCNL are required, as well as an in depth analysis of the hidden costs involved in unsuccessful URL treatments.

Introduction

Ureteral calculi are common, affecting more than 12% of the population and can have a serious impact on one's life and work[1,2]. The likelihood of spontaneously passing a ureteral stone is largely dependent upon the size and location of calculi[3]. While the majority of small distal stones can spontaneously pass through the ureter into the bladder before being expelled, large proximal ureteral stones (LPUS) with a diameter of 10mm or greater are unlikely to spontaneously pass, and can in the more severe cases become impacted in the ureter causing excruciating pain, urinary tract infections, hydronephrosis and renal dysfunction[3,4]. In this scenario, surgical interventions are recommended to remove upper urinary tract obstruction for patients whom have not benefitted from initial medical expulsive therapy or extracorporeal shock wave lithotripsy (ESWL)[5,6].

Minimally invasive techniques are under development whilst the miniaturization of endoscopic equipment has taken place over the past two decades. Therefore, treatment modalities have shifted with technological advancements, from open ureterolithotomy to modern endourologic procedures, such as laparoscopic ureterolithotomy (LU), percutaneous nephrolithotomy (PCNL) and ureteroscopic lithotripsy (URL)[7]. Even though each of these interventions are widely used in clinical practice, the superior LPUS treatment modality remains unknown. Previous comparative studies have yielded subtly different results and even evidence garnered from the highest levels of secondary data analysis have reached contradictory conclusions[1,4,8].

For example, Torricelli et al. conducted a meta-analysis in 2016 which included a total of 646 participants[8]. Their findings suggested that LU should be considered the first-line alternative for LPUS, having an higher stone-free rate (SFR) and equivalent complications compared to semi-rigid URL. However, this meta-analysis only included six randomized controlled trials (RCT) which compared only two techniques, despite the fact that other techniques were available at that time. Additionally, the authors appear to have overlooked heterogeneity and therefore lack critical insight. There have since been three further meta-analytical studies which included a greater number of studies, although the results and respective conclusions appear contradictory[4,9,10]. This may have occurred because the authors attempted to include all available studies, of which some were relatively low quality. Unfortunately, the conclusion derived from Wu et al.'s meta-analysis appears incongruous with their own findings. Their evidence also directly conflicts with Deng et al.'s meta-analysis which culminated in PCNL being recommended and a suggestion for further research into minimally invasive PCNL (mPCNL).

Discrepancies are common but this evidence base appears littered with divergent recommendations and relatively low-quality studies. Of course, urologists like other clinicians rely on experience and knowing one's patients and history but evidence should drive patient-practitioner consultations, and ultimately practice. As such, we sought to conduct a systematic review and meta-analysis of high-quality studies to assess the efficacy and safety of each of these interventions for LPUS. The overarching aim is to develop the evidence base and provide clearer recommendations to guide clinicians treating LPUS patients and for shared decision-making.

Methods

Literature search and article selection

A comprehensive review of RCTs concerning different interventions for LPUS was performed using biomedical meta-databases including PubMed, EMBASE and the Cochrane Library up until March 2020. The following MeSH terms and free text words were used: Large proximal ureteral stones (LPUS); Laparoscopic ureterolithotomy (LU); Percutaneous nephrolithotomy (PCNL); Ureteroscopic lithotripsy (URL); These search terms were used alone and in combination. Additionally, manual searches were commenced for references and citations included within pertinent reviews. Language was restricted to English, and the literature search/selection process was performed following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines [11].

Studies were included, if they met all of the following eligibility criteria: (1) Comparative RCTs concerning the efficacy and safety of different surgical managements (i.e., URL, LU or PCNL) for LPUS; (2) Adult participants without anatomical abnormality at the time of diagnosis; (3) Reported outcomes which included SFR, surgery-related complications, operation time, auxiliary procedure, the length of hospitalization, and; (4) Language was English and the full text was readily available.

Literature searching, selection and data extraction was carefully performed by two independent investigators (SL and BJ) which was then cross-checked by a third author. Any discrepancies were resolved through discussion. A flowchart representing the search and selection process is presented in Figure 1.

Quality assessment of the included studies

The levels of evidence for each selected article were evaluated independently by two reviewers (SL and BJ) based on criteria recommended by the Oxford Centre for Evidence-based Medicine[12]. The methodological quality of RCTs was assessed using the Jadad scale which attributes scores ranging from 0 to 5[13]. Again, discrepancies were resolved through discussion with a third author.

Data extraction

Patients' baseline characteristics were extracted together with perioperative data which includes SFR, operation times, length of hospitalization, auxiliary procedure, treatment cost and surgical-related complications, such as hemorrhage requiring blood transfusion, urine leakage, infection, ureteral injury (i.e., ureteral mucosal damage, perforation, false passage and laceration) and long-term stricture.

2.4 Statistical analysis

Continuous outcomes were evaluated using weighted mean difference (WMD). Results were expressed as risk ratios (RR) with corresponding 95% confidence intervals (CI) for dichotomous variables. I^2 calculations were used to assess hetetrogeneity, where I^2 >50 % was considered substantial. The random effects model was applied to combined individual effect-size estimates, under the assumption that the true effect of these interventions would differ between studies. Pooled effects were calculated using the z test and statistical significance was based on the standard $p<0.05$ threshold. Subgroup analysis was conducted to garner insight into the specificity of SFR according to follow-up duration. Sensitivity analysis were performed to assess the reliability of findings and to identify potential sources of heterogeneity. Publication bias was considered with a funnel plot. All data analyses were conducted with Review Manager (version 5.3).

Results

Characteristics of selected studies

The initial search strategy yielded 277 studies from the meta-databases combined. Our strict eligibility meant that 265 reports were eventually excluded. 12 RCTs focusing on three different LPUS interventions were included, involving 1416 participants. Of whom, 39.9% (n = 632) underwent URL, 38.7% (n = 361) PCNL, and 21.4% (n = 423) LU[1,14-24]. Patient and study characteristics including the surgical devices type, size and definition of stone free status are summarized in Table 1. As to the stone composition, only two included trails detailed reported this parameter. Kumar et al showed that the proportion of cystine stone is 3%[23]. Qi et al reported that the proportion of uric acid and cystine stone is 10.3% and 3.2%[18]. Overall, RCTs included in this meta-analysis can be considered of reasonably high quality with eight studies achieving a Jadad score of 3 and the remaining studies achieving a score of 4.

Meta-analysis of SFR

URL versus LU

Four studies compared the immediate SFR, four studies evaluated the 1-month SFR, and two studies assessed the 3-month SFR after surgery between URL and LU. Pooled results showed the immediate SFR (RR 0.65; 95% CI 0.47-0.91; *p*=0.01), 1-month SFR (RR 0.79; 95% CI 0.72-0.87; *p*<0.00001) and 3-months SFR (RR 0.79; 95% CI 0.71- 0.89; *p*<0.0001) in LU were significantly higher than URL (Fig.2A).

URL versus PCNL

There were five studies which compared immediate SFR and seven studies reported 1-month SFR after surgery between URL and PCNL. Pooled results indicate that both immediate SFR (RR 0.76; 95% CI 0.68-0.85; *p*<0.00001) and 1-month SFR (RR 0.88; 95% CI 0.82-0.96; *p*=0.002) for PCNL are significantly superior to URL(Fig.2B).

LU Vs. PCNL

There were two studies which reported immediate SFR and three studies reported the 1-month SFR postoperatively between LU and PCNL. Pooled results suggest that the two techniques have equivalent immediate SFRs (RR 0.85; 95% CI 0.61- 1.20; *p*=0.36) and 1-month SFR (RR 0.97; 95% CI 0.93-1.01; *p*=0.16) (Fig.2C).

Meta-analysis of complications

Ureteral injury

Pooling outcomes from the included studies suggests that URL has a significantly higher ureteral injury (e.g., ureter perforation or avulsion) rate compared to both LU (RR 5.27, 95% CI1.52-18.22, *p*=0.009; Fig.3A) and PCNL (RR 4.11, 95% CI 1.03-16.34, *p*=0.04; Fig.3B).

However, no ureteral injury cases were reported in either the LU and PCNL groups.

Urine leakage

This outcome was reported using four studies focusing on URL and LU. No urine leakage occurred in patients who received URL although there are 17 patients who reported as having urine leakage in the LU group. Pooled analysis showed that URL has a lower risk of urine leakage compared to LU (RR 0.12, 95% CI 0.03–0.53, p=0.005; Fig.3C). However, no significantly difference was found between PCNL and LU (RR 0.62, 95% CI 0.09-4.22, p = 0.63; Fig.3D).

Hematuria

Only two studies comparing URL and PCNL could be included in this meta-analysis. The overall result was however, statistically significant and appears to support the use of URL (RR 0.27, 95% CI 0.14-0.53, p=0.00001; Fig.3E).

Blood transfusion

Pooled results from the two studies which reported this outcome suggests that there is no significant difference between URL and PCNL regarding this parameter (RR 0.18, 95% CI 0.02-1.44, p=0.11; Fig.3F).

Other complications

Results of this meta-analysis did not detect significant differences between URL and LU in terms of postoperative pain, fever, open conversion and ureteral stricture. Pooling also demonstrated that URL and PCNL had similar complication rates regarding postoperative pain, fever, open conversion and ureteral stricture. In addition, there were no significant difference between PCNL and LU in terms of postoperative fever (All p >0.05). Please see Figure 4. and Table 2. for further details.

Meta-analysis of perioperative parameters

Operative time

Seven studies directly compared URL against LU in terms of operation times. Overall, URL takes less time than LU (WMD -33.48 minutes, 95% CI -48.21 to -18.76, *p*<0.00001; Fig.5A). No significant difference was found between URL and PCNL (WMD -18.55 minutes, 95% CI -46.82 to 9.72, *p*=0.20; Fig.5B). Similarly, no significant difference was observed between PCNL and LU (WMD -14.40 minutes, 95% CI -49.80 to 21.00, *p*=0.43; Fig. 5C).

Hospitalization time

Combined evidence showed that the URL is related to significantly shorter hospitalization times compared to LU (WMD -1.73 days, 95% CI -3.29 to -0.17, *p*=0.03; Fig.5D) and PCNL (WMD -3.33 days, 95% CI -4.01 to -2.65, *p*<0.00001; Fig.5E). And when combined, three studies involving 290 participants suggested that there was no substantial or significant difference between PCNL and LU (WMD 1.09 minutes, 95% CI -1.52 to 3.70, *p*=0.41; Fig. 5F).

Treatment cost

There were only two studies which had compared treatment costs between the PCNL and URL. The combined result suggests that the URL is substantially and significantly cheaper than PCNL (WMD -597.35 US$, 95% CI -823.10 to -371.60, *p*<0.00001; Fig.6A).

Stone retropulsion

This outcome was reported in only three studies which focused on URL and LU. Pooled analysis suggests that URL is related to an higher risk of stone retropulsion compared to LU (RR 2.82, 95% CI 1.10–7.22, *p*=0.03; Fig.6B)

Auxiliary treatment

This parameter was reported in two studies focusing on URL and LU. Pooled analysis indicated that URL has an higher risk of repeat or auxiliary treatment compared to LU (RR 15.65, 95% CI 2.11–116.12, *p*=0.007; Fig.6C). Similarly, pooling four of the included studies suggests that URL is associated with a significantly higher auxiliary treatment rate compared to PCNL (RR 8.86; 95% CI 3.19-24.60; *p*<0.00001; Fig.6D).

Risk of bias

The basic symmetry of the generated funnel plots suggests that there was no obvious publication bias in this meta-analysis (Fig. 7).

Discussion

Identifying the optimal therapy for LPUS requires decision makers to consider a number of factors including safety, efficacy, resources, recovery time and cost[9,23,25]. ESWL has been recommended as the first choice for small upper ureteral calculi with a diameter of less than 10mm by the European Association of Urology guidelines[7]. This guideline is broadly based on the non-invasive nature of ESWL, which is also relatively inexpensive; however, this intervention is not without disadvantages. ESWL is frequently ineffective and therefore has an higher demand for re-intervention, especially for stones larger than 10 mm[1,7,15,26]. As such, the current recommendations for larger impacted stones include URL, LU and PCNL.

Ureteroscopic lithotripsy originally emerged as a promising intervention and attracted attention because it is considered minimally invasive, and also associated with a considerable stone-free rate[19,27]. Presently, both the European Association of Urology and the American Urology Association recommend URL as one possible first-line therapy for mid- and distal ureteral calculi[7,28]. Consequently, patients tend to be keen on this intervention because this is no doubt discussed during the shared decision-making process between patient and practitioner. However, regarding its ability to treat LPUS, several studies have found that URL has a low success rate, between 62.5-79%[14,15]. Our meta-analysis appears to confirm that URL is not as effective as either, PCNL or LU. Another issue to be considered is that URL also appears to be associated with an increased number of ureteral injuries which include ureteral mucosal damage, perforation, false passage and even laceration[4].

When we consider the ureteral injuries related to URL, we need to specifically consider stone retropulsion which can occur during the procedure[18,29]. The majority of LPUS are located near the renal pelvis, therefore fragment migration occurs in as many as 60% of all cases because of the flushing fluid process involved in URL. This means that a large number of residual stones become distributed within the renal peli-calyceal system[19]. Secondly, because impacted proximal stones are usually associated with ureteral mucosal edema, stenosis or fibrous epithelial polyps, it is comparatively difficult to access these stones using ureteroscopic technologies, especially in patients with a narrower ureter ostium or with a more fragile/narrow ureter[15,25].

Certainly, a flexible ureteroscope, which has a smaller diameter and more flexible neck can be inserted without further dilation[14]. This means, a flexible ureteroscope can be used to treat proximal stones and retrieve debris which appears to be effectively migrating into the renal calyx[30,31]. Cavildak et al. once performed a study comparing the effectiveness of LU and flexible URL in patients with LPUS. The results indicated that success rates of LU can be up to 95.7%[32]. However, these specialized devices are relatively expensive, meaning they are not widely available[9,33,34]. Among all 12 included RCTs included, only two studies involving 55 patients, used this specialized device. Also, as with all things new, there is a learning curve and experience tells us that using the flexible ureteroscope takes longer to master. Given these barriers, and the fact that a ureteroscope (either flexible or rigid) may not be able to reach a stone which have moved into the calyx, one might suggest there is a need for further economics research which intercalates secondary operations when initial attempts fail. This knowledge is particularly necessary for developing countries with fewer healthcare resources.

Another minimally invasive lithotripsy technique investigated here was laparoscopic ureterolithotomy which gained similar popularity since its introduction because of the potentially complete stone clearance rates after a single attempt[14,23]. Additionally, while obstructive stones are often associated with severe urinary tract infections, LU appears capable of their safe removal because this surgical procedure does not require high pressure of perfusion. Several studies have also demonstrated that LU can provide a fewer severe complications such as bleeding and ureteral stricture at long-term follow-up[14,15,35]. However, LU has its shortcomings, like most of laparoscopic operations, serious trocar-related damages including damage to abdominal organs and vascular injuries may occur if the pneumoperitoneum or abdomen distension are insufficient. This technique is comparatively technical and therefore requires surgeons with advanced skills[1,16]. This is because LU is associated with an increased number of bowel, kidney and abdominal vascular damage. As larger impacted stones involve periureteral adhesions, dissection can increase the risk of urinary leak, paralytic ileus and postoperative pain, which are particularly disadvantageous in terms of postoperative rehabilitation[16]. In current study, there were 17 patients who reported having urine leakage in the LU group, two of whom required a Double-J catheter insert as an auxiliary procedure. Consequently, clinicians generally consider laparoscopy as an alternative technique.

Baring these issues in mind and the current evidence, PCNL appears to be the most favorable technique for the management of LPUS. This is likely to be the result of enhanced viewing through fluroscopy or ultrasound technologies. After accurately penetrating the kidney with the needle and safely positioning a small working sheath in the collecting system through a small lumbar skin incision, stones can be easily observed, reached and then effectively cleared.

These characteristics enable those administering PCNL to simultaneously manage renal stones, and to achieve higher stone-free rates with less risk of injury[36,37]. The pooled results of this study suggest that PCNL has an equivalent stone clearance rate to LU while being superior to URL.

Furthermore, there were no significant differences between the PCNL and LU regarding surgery time or length of postoperative hospitalization. Though PCNL has been criticized for having an higher risk of hemorrhage when establishing an intrarenal channel, this disadvantage can be solved by upgrading the standard PCNL equipment and then slightly modifying the surgical technique[21,36]. mPCNL requires only a miniature endoscope instead of the 26F–30F nephroscope used in standard PCNL[21,37,38]. This simple upgrade creates a smaller, less intrusive device which can provide a strong safety profile while achieving good SFR. Evidence suggests that the incidence of bleeding which requires transfusion and other peri-operative complications rate were significantly lower than standard PCNL[20].

According to this meta-analysis, PCNL and LU appear equal in terms of stone free rate, and are both superior to URL. PCNL and LU are associated with fewer complications than URL, and are again not dissimilar when compared directly. However, URL is associated with a shorter operation time and shorter periods of hospitalization. Of course, this has financial implications which cannot be overlooked. URL costs significantly less than both PCNL and LU; although, it is essential to consider that between 25-30% patients who receive URL require auxiliary procedures (i.e., ESWL or flexible ureteroscopy) postoperatively since URL is generally unable to completely remove calculus in a single procedure[34,39]. According to previous studies, the average estimated added cost of auxiliary interventions for residual stones ranges from $5840 to

$6118[18,40]. Therefore overall, PCNL appears to be the most efficient and effective choice for treating LUPS.

This meta-analysis was designed to include all currently available RCTs; however, there were of course some limitations. First of all, all the included RCTs did not follow the principles of double-blinding due to ethical concerns in surgical trials. This is likely to have influenced the quality of this evidence and therefore our recommendations remain tentative. Secondly, not all patients' postoperative stone status was evaluated using computer tomography. This is likely to have increased the overall stone-free rate, given the low sensitivity of traditional radiography in detecting radiolucent or smaller calculus. Additionally, the precise definition of 'stone-free' does not appear consistent across all studies, but this is also probably part of the reason for the high heterogeneity observed. Furthermore, even though flexible ureteroscopy has many advantages, few published RCTs have been conducted comparing this technique to PCNL or LU, thus preventing us from including flexible ureteroscopy into this systematic evaluation.

Conclusions

Both PCNL and LU appear more effective and safer than URL for LPUS; although, LU has higher risk of urine leakage and is more likely incur trauma which requires additional support. However, caution must be taken because this recommendation is based upon a very limited number of clinical studies, and even fewer comparing flexible ureteroscopic technologies. Further prospective real-world studies or RCTs comparing flexible URL, LU and PCNL are required, as well as an in depth analysis of the hidden costs involved in unsuccessful URL treatments.

Ethical approval

Ethics committee approval was not necessary because all data were carefully extracted from existing literature, and this article did not involve handling of individual patient data. In addition, neither patients nor the public were involved in the design and planning of the study.

Consent for publication

Not required

Sources of funding

As the journal operates a double-blind peer review policy, the funding details were removed from current version.

Unique identifying number (UIN)

This study is registered with the Research Registry and the unique identifying number is: reviewregistry854.

Conflict of interest

The authors declared that this study has received no financial support and that there was no conflict of interest.

Availability of data and materials

Not applicable

Provenance and peer review

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Figure legends

Fig. 1 Flowchart of study selection

Fig. 2 Forest plots comparing: (A) SFR between URL and LU, (B) SFR between URL and PCNL, (C) SFR between LU and PCNL

Fig. 3 Forest plots comparing: (A) ureteral injury between URL and LU, (B) ureteral injury between URL and PCNL, (C) urine leakage between URL and LU, (D) urine leakage between LU and PCNL, (E) hematuria between URL and PCNL, (F) blood transfusion between URL and PCNL.

Fig. 4 Forest plots of other complications including: (A) postoperative fever between URL and LU, (B) urinary tract infection between URL and LU, (C) ureteral stricture between URL and LU, (D) postoperative pain between URL and LU, (E) open conversion between URL and LU, (F) postoperative fever between URL and PCNL, (G) ureteral stricture between URL and PCNL, (H) postoperative pain between URL and PCNL, (H) open conversion between URL and PCNL, (I) postoperative fever between PCNLL and LU.

Fig. 5 Forest plots comparing: (A) operation time between URL and LU, (B) operation time between URL and PCNL, (C) operation time between PCNL and LU, (D) hospitalization time between URL and LU, (E) hospitalization time between URL and PCNL, (F) hospitalization time between PCNL and LU.

Fig. 6 Forest plots comparing: (A) cost between URL and PCNL, (B) stone retropulsion between URL and LU, (C) auxiliary treatment between URL and LU, (D) auxiliary treatment between URL and PCNL.

Fig. 7 Funnel plot for assessing publication bias

Table 1. Study characteristics and quality assessment

Authors and year	Country	Study period	Study design	Group	Sample size	Age (years)	Stone size	Devices	Lithotripsy method	SFS evaluation method	SFS definition	Follow-up period	Jadad scores	LE
Wang et al. 2017	China	2012.1-2015.12	RCT	MPCNL	50	41±15	19.3 ± 1.8 mm	18F Access sheath size	Swiss lithoclast	X-ray	no stone≥4 mm	1 month	3	2a
				URL	50	42±14	16.8 ± 2.1 mm	8F/9.8F Rigid	Laser					
				LU	50	44±11	18.8 ± 1.4 mm	Retroperitoneal						
Kumar et al. 2015	India	2010.1-2012.5	RCT	URL	50	35.6±2.1	2.2 ±0.1 cm	6/7.5 Fr Semi-rigid	Laser	CT		3 months	3	2a
				LU	50	36.7±2.4	2.3 ± 0.2 cm	Transperitoneal						
Shao et al. 2015	China	2009.1-2013.10	RCT	URL	139	41(23-72)	13.6 ± 1.4 mm	8F Semi-rigid	Laser			Not mentioned	3	2a
				LU	136	40(22-72)	13.8 ± 1.9 mm	Retroperitoneal						
Qi et al. 2014	China	2010.5-2013.5	RCT	URL	52	42.5±10.3	19.8±4.3 mm	8F/9.8F Semirigid	Pneumatic/Laser	X-ray or US	no stone≥4 mm	3 days/1 month	3	2a
				PCNL	52	41.1±12.4	20.3±3.6 mm	20.8F Access sheath size	Ultrasonic and Pneumatic					
Gu et al. 2014	China	2010.9-2011.12	RCT	MPCNL	30	42.5±10.1	17.27(15-25) mm	12F–18F Access sheath size	Laser	X-ray	no stone≥4 mm	2 weeks/ 1 month	4	2a
				URL	29	44.22±13	16.23(15-25) mm	8.5/9.8F Semi-rigid/ Flexible	Laser					
Ozturk et al. 2013	Turkey	2015.3-2015.9	RCT	URL	48	41.1(24-58)	13.2±2.04 mm	Flexible ureteroscopy	Laser	X-ray or US	no stone≥4 mm	3 months	3	2a
				LU	51	40.4(19-62)	13.3±2.06 mm							
Liu et al.	China			MPCNL	45	46.35±10.31	146.85±30.36 mm^3		Laser	X-ray	no	3 days/1	4	2a

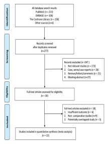
2013		2012.1-2015.12	RCT	URL LU	45 45	43.41±10.17 44.73±10.56	148.13±27.52 mm^3 149.16±32.15 mm^3	Rigid Retroperitoneal	Laser		stone≥4 mm	month		
Yang et al. 2012	China	Not mention	RCT	MPCNL URL	91 91	45.2±14.7 46.4±15.1	158.7 ± 96.8mm2 134.2 ± 83.3 mm2	16F Access sheath size 8/9.8F Rigid	Laser Laser	X-ray or US	no stone≥4 mm	3 days/1 month	4	2a
Fang et al. 2012	China	2008.1-2010.12	RCT	URL LU	25 25	36.9±11.8 34.44±9.8	1.5±0.4 cm 1.6±0.3 cm	8/9.8F Rigid Retroperitoneal		X-ray	no stone≥4 mm	1-2days	3	2a
Antonio et al. 2011	Brazil	2008.3-2010.3	RCT	URL LU	16 15	49.6±15.5 46.0±13.6	14.4±4.1mm 15.9±4.1mm	7.5F Semi-rigid Trans-/retroperitoneal	Pneumatic	X-ray/ CT	no stone≥3 mm	1week/ 4 weeks	4	2a
Basiri et al. 2008	Iran	2004.9-2006.5	RCT	PCNL URL LU	50 50 50	48±13 39±15 44±13	20.3 ± 3.3 mm 17.8 ± 2.4 mm 22.4 ± 3.2 mm	 7.8F Semi-rigid Transperitoneal	Laser Pneumatic/ Laser	X-ray/ US		3 weeks	3	2a
Sun et al. 2008	China	2004.7-2006.12	RCT	MPCNL URL	44 47	40.4±8.4 39.6±7.3	14.7 ± 2.0 mm 14.6 ± 1.8mm	14F - 16F Access sheath size 8.5/9.8F Semi-rigid	Laser Laser	X-ray/ CT	no stone≥5 mm	discharge/ 1 month	3	2a

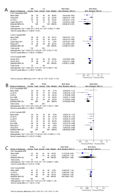
PCNL=percutaneous nephrolithotomy; CT=computed tomography, US=ultrasound; ESWL=extracorporeal shock wave lithotripsy; LU=laparoscopic ureterolithotomy; MPCNL=minimally invasive percutaneous nephrolithotomy; URL=transurethral ureteroscope lithotripsy; LE=level of evidence; RCT=randomized controlled trial

Comparision	SFR	Ureteral injury	Urine leakage	Hematuria	Fever	Open conversion	Pain	Ureteral infection	Ureteral stricture	Transfusion	Surgery time	Hospitalization	Cost	Auxiliary treatment
URL vs LU	LU> URL	URL> LU	LU> URL	-	N	N	N	N	N	-	LU> URL	LU> URL	-	URL > LU
URLvs PCNL	PCNL >URL	URL> PCNL	-	URL> PCNL	N	N	N	-	N	N	N	PCNL> URL	PCNL>URL	PCNL> URL
PCNL vs LU	N	N	N	-	N	-	-	-	-	-	N	N	-	-

PCNL=percutaneous nephrolithotomy, N=not significant difference，LU =laparoscopic ureterolithotomy; MPCNL=minimally invasive percutaneous nephrolithotomy; URL=transurethral ureteroscope lithotripsy; “-” =not mentioned; “>” =superior

Table 2. Outcome parameters


Identification
All database search results
PubMed: (n = 213)
The Cochrane Library: (n = 158)
Other sources (n=6)
Screening
Records screened
after duplicates removed
(n=277)
Records excluded (n =247)
1. Not relevant studies (n = 173)
2. Case, series/case reports (n = 26)
3. Reviews/letters/comments (n = 21)
4. Meeting abstract (n=27)
Eligibility
Full-text articles assessed for eligibility
(n = 30)
Full-text articles excluded (n = 18)
1. Insufficient outcome (n = 6)
2. Non-comparative studies (n=9)
3. Potentially overlapped study (n = 3)
Included
Studies included in quantitative synthesis (meta-analysis)
(n = 12)


A
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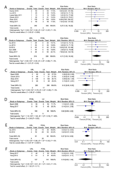

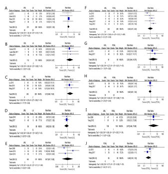

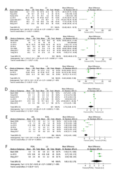

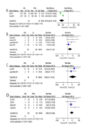

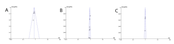

Highlights

- Both percutaneous nephrolithotomy (PCNL) and laparoscopic ureterolithotomy (LU) appear more effective and safer than ureteroscopic lithotripsy (URL) for large proximal ureteral stones (LPUS).
- LU has higher risk of urine leakage.
- LU can incur more trauma than PCNL and should be recommended as an alternative technique for LPUS.

Data statement

All the data were presented in the manuscript. No additional data are available.