

## ANNOTATION

of PhD thesis by Mami Darkhan Erlanuly on the topic «**Minimally invasive endoscopic methods for treating patients with urolithiasis**», submitted for the degree of Doctor of Philosophy (PhD) in the specialty 6D110100 – «Medicine»

**Relevance of the research topic:** Urolithiasis (ULA) among urological diseases is one of the most common, affecting males and females at any age, most often people of working age suffer. In this context, both the creation and refinement of new surgical treatment techniques as well as the investigation of various preventative and metaphylaxis measures remain important. Annual reviews of the European Association of Urology's guidelines and clinical recommendations for the treatment of urolithiasis have shown that extracorporeal shock wave lithotripsy (ESWL) and percutaneous nephrolithotripsy (PNLT) are the most frequently advised minimally invasive procedures for kidney stone removal. The "gold" standard for the treatment of stones under 2 cm is ESWL, and some authors claim that its efficacy rate can exceed 90%. The effectiveness of ESWL depends on many factors: localization of the calculus, size, density. This method is of little use for stones larger than 2 cm.

PNLT has the highest efficiency in the treatment of calculi larger than 2 cm, including staghorn ones. According to Singla M. et al. (2008), the effectiveness of PNLT in staghorn calculi ranges from 74 to 83%. Preminger G. (2005) and Michel M. (2007) indicate the effectiveness of this treatment method from 78-95%. However, it has been reliably proven that PNLT is accompanied by a high risk of complications such as bleeding, urosepsis.

With the improvement of endourological equipment, the introduction of flexible ureteroscopes and laser lithotripters, in 2005 it began to be actively introduced as an alternative method - retrograde pyelolithotripsy (RPT). To date, there are studies in the literature on the study of the effectiveness of RPT, including in a comparative aspect with other minimally invasive methods of treating ULA.

The results of the use of RPT by foreign researchers are still contradictory. For example, Perlmutter et al. when studying the effectiveness of RPT for kidney calculi up to 2 cm in size of different localization, it indicates 100% effectiveness of the method for calculi of the upper groups of calices, 95.8% efficiency for the localization of calculi in the middle groups of calyces and 90.9% efficiency for calculi of the lower calices of the kidneys.

Traxer O. et al. 445 patients were enrolled in the study of the efficacy of RPT. The average duration of the operation was 82.5 minutes (28-215 minutes). The average size of the calculus is 25 mm. The overall complication rate was 10.1%. Major complications were observed in 21 (5.3%) patients and minor complications developed in 19 (4.8%) patients. The analysis showed that the RPT method has 95.7% of kidney cleansing from calculi, up to 2-3 cm in size and 84.6% in cases where the calculus is > 3 cm ( $p = 0.01$ ), with an insignificant number of complications 14.3 % and 15.4%, respectively, and the main complication rate of 0% and 11.5%, respectively.

Thus, despite the introduction of new and continuous improvement of existing endoscopic methods and treatment methods, this problem remains relevant, especially in regards to the sequence of their use and the combination of various methods.

**Purpose of the study.** To substantiate the method of combined endoscopic treatment in patients with nephrolithiasis and ureterolithiasis, depending on the size, location and density of the calculus in urolithiasis.

**Research objectives:**

1. To compare the effectiveness of endoscopic methods for the treatment of nephrolithiasis and ureterolithiasis. Retrograde pyelolithotripsy (RPT), percutaneous nephrolithotripsy (PNLT) and a combined method of treatment depending on the size, location and density of the calculus in urolithiasis.

2. To study the effectiveness of retrograde pyelolithotripsy in the treatment of staghorn, large and multiple calculi.

3. To determine the optimal endoscopic method for the treatment of nephrolithiasis, depending on the size, location and density of the calculus in urolithiasis.

**Methodology and research methods.** An evaluation of the merits of minimally invasive endoscopic urolithiasis treatments was part of the research methodology. The concepts of evidence-based medicine, including patient selection, statistical processing of research findings, clinical, laboratory, and instrumental research methodologies, are applied in the study to address a number of issues in the dissertation research.

**Objects and methods of research:**

Patients treated between December 2017 and December 2018 at the Department of Urolithiasis and Endourology of JSC «Scientific Center of Urology named after Academician B.U. Dzharubynov» ranged in age from 18 to 75. 144 individuals (of whom 81 were women and 63 were men) with urolithiasis, including difficult types such as bilateral nephrolithiasis, staghorn, massive and numerous calculi of the kidneys and ureter.

Left-sided localisation of calculi was observed in 58 cases, or 40.28% of the total. 63 individuals, or 43.75%, had calculi that were localized on the right side. A bilateral process was observed in 23 cases, or 15.97%, of the total.

Depending on the type of surgical intervention performed, the patients were divided into groups:

group 1 - patients who underwent retrograde pyelolithotripsy (74);

group 2 - patients who underwent percutaneous nephrolithotripsy (52);

group 3 - patients who underwent a combined method of treatment (18).

This group included two subgroups, depending on the stages of the treatment.

A) patients who simultaneously underwent a combined method (10).

B) patients in whom the combined method was performed in 2 stages (the first stage is percutaneous nephrostomy or placement of a stent catheter (8).

When patients were included in this study, absolute and relative indications and contraindications for surgical treatment of urolithiasis using endoscopic methods were taken into account. According to these indications and contraindications, criteria for inclusion and exclusion of patients in the study were developed. As well as carrying out metaphylaxis is divided into the period of early postoperative metaphylaxis and the period of dynamic metaphylaxis of the ULA.

**Inclusion Criteria:**

- patients with nephro-ureterolithiasis who are indicated for surgical treatment using endoscopic technologies (retrograde pyelolithotripsy and percutaneous nephrolithotripsy) in a planned manner;
- informed voluntary consent of patients for examination and treatment in accordance with the Declaration of Helsinki.

**Exclusion Criteria:**

- age up to 18 years;
- chronic kidney disease (CKD) 4-5 stages;
- acute renal failure (ARF);
- liver failure;
- diabetes mellitus, in the stage of decompensation;
- chronic pulmonary heart failure;
- malignant (intractable) arterial hypertension;
- acute inflammatory diseases of the kidneys and urinary tract;
- oncological pathology of any localization in the active stage;
- diseases associated with impaired blood clotting.

**Tasks of early postoperative metaphylaxis:**

1. fight against inflammatory changes in the kidney, surrounding tissues and urinary tract;
2. stimulation of the discharge of disintegrated fragments of the calculus.

The first stage seems to us lasting up to 3 months, there is the formation of sclerotic changes in the kidney and the surrounding tissue, due to both the operational aid itself and its complications. It was during this period, in the presence of changes in the perirenal tissue, in the pelvic-ureteral segment, the detection of urinary tract dyskinesia, that it is possible, by carrying out conservative therapeutic measures, to avoid the formation of irreversible, due to organic causes, urodynamic disorders that contribute to the progression of chronic pyelonephritis and recurrence of stone formation.

The second stage of observation (dynamic metaphylaxis) should continue throughout the patient's life.

**Endoscopic treatments:**

**Percutaneous nephrolithotripsy**

Percutaneous nephrolithotripsy (PNLT) is a minimally invasive method for the treatment of ULA with single, multiple, large and staghorn calculi. PNLT consists of 2 stages: creation of antegrade puncture access to the kidney and removal of the calculus through this nephrostomy passage. Removal of stones is carried out under X-ray and endoscopic control. The operation ends with drainage of the kidney with a nephrostomy tube (nephrostomy No. 18-20).

**Retrograde pyelolithotripsy**

Retrograde pyelolithotripsy (RPT) is based on the destruction of urinary tract calculi with direct visual contact between the lithotripter probe and the calculus, while access to the calculus is carried out retrogradely, through the natural urinary tract, without violating the integrity of the skin. The cavity system is drained by the installation of a stent catheter (6/26). The bladder is drained with a urethral catheter, which is removed 1-2 days after surgery.

**Combined treatment method**

The combined method (RPT+PNLT) is a highly effective method of treatment that allows, within the framework of one anesthesia, in one surgical intervention, to rid the patient of the calculi of the indicated localizations. The indisputable advantage of this method is the reduction of hospitalization time and the rapid social rehabilitation of the patient, as well as access to any localization of the calculus. With complete evacuation of calculi from the cavitory system, the nephrostomy is not installed; a stent catheter is installed antegrade to drain the cavitory system of the kidney.

#### **Basic provisions for defense:**

1. The results of the use of retrograde pyelolithotripsy, percutaneous nephrolithotripsy and a combined endoscopic method in the treatment of nephroureterolithiasis allows us to testify to the effectiveness of the use of minimally invasive surgical interventions in patients with urolithiasis.

2. The results of evaluating the effectiveness of the use of minimally invasive surgical interventions allow us to assert a significant improvement in the quality of life of patients, a reduction in complications, the duration of surgical intervention and hospitalization.

3. Simultaneous use of various accesses to the kidney with the combined endoscopic method, within the framework of one anesthesia, in one surgical intervention, relieves the patient of stones from the kidney and/3 of the ureter. The undeniable advantage of this method is the reduction of hospitalization time and rapid social rehabilitation of the patient.

4. The results of assessing the quality of metaphylaxis of urolithiasis.

#### **Statistical analysis**

Statistical analysis was performed using SAS University Edition, version 3.8 (SAS Institute Inc., Cary, NC, USA). Categorical variables were expressed as frequency and percentage. We used the chi-square test and Fisher's exact test to evaluate differences and associations between variables. Continuous variables were expressed as mean and standard deviation (SD) and were analyzed using one-way ANOVA. The Kruskal-Wallis test was used to compare non-normally distributed continuous variables and those presented as a median (interquartile range). We used logistic regression to estimate the crude and adjusted odds ratios. (OR) and 95% confidence intervals (CI) for associations between potential risk factors and stone-free rates, intra- and postoperative complications. The alpha level has been set to 0.05, considering it to be statistically significant.

#### **Research results**

*Results of treatment of retrograde pyelolithotripsy.* Out of 74 patients, 37 patients (50%) had calculi up to 1.5 cm, 23 patients (31%) had calculi between 1.6 and 2 cm, and 14 patients (19%) had calculi up to 3 cm. Patients who had calculi with structural densities between 801 and 1,900 HU had RPT with good results; the procedure took an average of 55.94 26.50 minutes. Due to the inability to completely fragment the calculus, RPT was ineffective in 12 cases (16.22%) and successful in 62 situations (83.78%). Remaining fragments in a size range of 2 to 4 mm left on their own after RPT. Urinary strictures were found in 1 observation (1.35%) and ureteral kinks in 2 cases (2.7%). Two patients underwent endoscopic bougienage of the ureteral stricture with the installation of a stent catheter, with further replacement of the stent catheter

after 1 month, which was removed after 1 month. One patient underwent ureteropyeloplasty with internal drainage. As a result of the treatment, after 1 month in these 3 patients with complications, the passage of urine was completely restored. Complications such as exacerbation of chronic pyelonephritis after RPT were noted in 5 patients (6.76%).

According to the study's findings, treatment effectiveness after surgery was 83.78%, and the clinical efficacy of therapy, evaluated 4 weeks after RPT, was 92%. The number of successful RPTs we performed also leads us to believe that this procedure is more effective in removing stones up to 3 cm.

*Results of treatment of percutaneous nephrolithotripsy.* When determining indications for PLNT, out of 52 patients with ULA from 1.6–2 cm, calculi occurred in 7 cases (13.46%), from 2.1–3 cm were in 11 patients (21.1%), from 3.1 - 4 cm. stones in 14 cases (26.9%), from 4.1 - 5 cm in 8 patients (15.3%) and in 12 persons from 5.1 - 6 cm. 23.0%. 52 patients, where 24 patients (46.1%) had a staghorn calculus (K-1, K-2, K-3), removal of calculi in the right kidney in 18 patients (34.6%) and in 10 cases (19, 2%) had calculi in the left kidney.

In 23 patients (44.2%), when the size of the calculus did not exceed 2.1 - 4.0 cm, the calculi were removed entirely, in 11 patients (21.1%), the calculi were removed (for larger calculi) after preliminary contact lithotripsy. After PNLNT, migration of fragments of staghorn calculus into the ureter was observed in 3 patients (5.7%), and they finally underwent ureterolithoextraction.

In the early postoperative period, postoperative complications were not observed in 42 patients (78.85%). After PNLNT in 10 cases (19.23%) high fever and hematuria were observed, and in 9 cases (17.31%) there was an exacerbation of chronic calculous pyelonephritis. 2 patients (3.85%) underwent hemotransfusion with PCNLNT. Patients with complications after PNLNT received appropriate conservative therapy.

After PNLNT, 3 patients were found to have residual calculi from 5 to 10 mm in diameter, and then these patients underwent one session of ESWL with a positive effect. As a result of the study with PNLNT, it was found that in patients according to the Stone free rate criterion, the effectiveness of treatment was 78.85%. The clinical efficacy of treatment, estimated 4 weeks after PNLNT, was 91%.

*Results of treatment of the combined method of nephro- and ureterolithiasis.*

The combined method proposed by us makes it possible to treat patients with clinically complex variants of nephrolithiasis (large, dense, multiple, recurrent, X-ray negative, staghorn calculi, as well as patients with anomalies of the upper urinary tract and the only functioning kidney). The advantage of the method is the minimization of operational access while maintaining an adequate amount of intervention. With the combined method, retrograde pyelolithotripsy is performed first, so the patient is first placed on his back, the operation is performed under spinal anesthesia. After the end of pyelolithotripsy, a ureteral stent is installed and the patient is transferred to the stomach for percutaneous nephrolithotripsy. With complete evacuation of stones, the nephrostomy is not installed after the operation, only a stent catheter remains for drainage of the urinary tract and kidney.

The main indications for the combined method were large (more than 5.0 cm) and dense (more than 1000 HU and more) kidney calculi, as well as in complex clinical forms of urolithiasis and the presence of single calculi in/3 of the ureter and pelvis or lower calyx.

After the end of the first stage of treatment, pyelolithotripsy, a ureteral catheter or stent catheter is installed, this helps to prevent the migration of stones into the ureter during percutaneous nephrolithotripsy.

In this group, the average operation lasted  $58.88 \pm 13.12$  minutes.

After the combined operation, in 17 patients (94.44%), the cavitory system of the kidneys and ureter was completely free of calculi (Stone-free rate). The remaining 1 patient (5.5%) had residual stones. This patient underwent an additional ESWL session.

There were no intraoperative complications requiring open surgery. One patient underwent percutaneous nephrolithotripsy with two accesses. Infectious-inflammatory complications were noted in 3 patients (7.3%), and were stopped conservatively.

As a result of the study in patients of the 3rd group (combined method), according to the Stone free rate criterion (complete cleansing of the kidney from stone and its fragments), the effectiveness of treatment was 95%, and the clinical effectiveness of treatment, assessed after 4 weeks, was 95%.

**Implementation of research results.** The results of the dissertation research have been introduced into the practical work of the Department of Urolithiasis and Endourology of JSC «Scientific Center of Urology named after B.U. Dzharbusynov».

**Scientific novelty:**

1. The efficiency of the combined endoscopic approach based on the combination of retrograde pyelolithotripsy and percutaneous nephrolithotripsy for multiple and big kidney stones was assessed in patients with nephroureterolithiasis.

2. The efficiency of the various metaphylaxis stages of stone creation is evaluated, and their future prospects are identified.

**Practical significance.**

1. As a result of the introduction of minimally invasive surgical interventions into clinical practice, with urolithiasis, the quality of life of patients in the postoperative period has significantly improved, the frequency of complications has decreased, the duration of surgical intervention has decreased, and the duration of hospitalization has been reduced.

2. Based on the analysis of the use of minimally invasive surgical interventions, it was possible to avoid repeated operations, which significantly improved the quality of life of patients, reducing the frequency of complications and the duration of surgical intervention, and the duration of hospitalization.

3. The advantage of the combined RPT+PNLT method, the simultaneous use of minimally invasive methods in complex clinical cases, which made it possible to determine the indications and contraindications for this method, has been proven.

4. A high percentage of clinical cases with complete elimination of calculi was achieved after one operation with combined surgery, as a result of which the number of repeated hospitalizations decreased.

**Practical recommendations**

1. When removing stones with a size of 1.5 to 3 cm and a density of 801-1.900 units. H.U. RPT should be considered as a method of choice for the first line of surgical treatment.

2. The introduction of the combined endoscopic method has significantly reduced the time spent in the hospital and rehabilitation of patients, preventing patients from

repeated hospitalizations and operations when removing both kidney calculi and ureteral calculi.

3. Using a combined minimally invasive endoscopic technique, it is possible to remove complex and dense kidney and ureter stones within one anesthesia, in one surgical intervention.

4. Based on the clinical efficacy after minimally invasive endoscopic surgical interventions in terms of achieving the final and favorable result (Stone free rate), it is recommended to use this surgical technique in hospitals of the Republic of Kazakhstan for patients with complicated forms of nephrolithiasis.

**The author's personal contribution** is to substantiate the direction of the research; creating the format and design of the study; organizing and conducting all its stages; collection, processing and analysis of data; design, presentation and discussion of the results of the dissertation. The author personally formulated the goals, objectives of the study, the provisions submitted for defense; introduced a combined method (retrograde pyelolithotripsy + percutaneous nephrolithotripsy) in patients with nephro-ureterolithiasis. The substantiation of the methodology for introducing a new method, the formulation of conclusions, the preparation of practical recommendations and proposals for implementation belongs personally to the author.

### **Conclusions**

1. Comparative evaluation of minimally invasive endoscopic surgeries interventions showed that the clinical efficacy of treatment averaged 92.7% ( $p > 0.05$ ) for all study groups. After RPT - 92% ( $p > 0.05$ ), after PNLT - 91% ( $p > 0.05$ ) and after the combined method - 95% ( $p > 0.05$ )

2. With retrograde pyelolithotripsy, stones from 1.5 cm in size, with an average structural density of 801-1.900 HU are safely and effectively removed compared to calculi ( $>3$  cm) and groups 2 and 3.

3. When comparing endoscopic research methods (RPT and PNLT), combined method of treatment of nephrolithiasis and ureterolithiasis showed a high percentage of the patient getting rid of calculi (95%) and can reduce the duration of hospitalization

### **Approbation of work**

The main provisions of the work were reported and discussed at:

1. At the 4th Scientific and Practical Conference of Urologists of the Northwestern Federal District of the Russian Federation. April 19 – 20, 2018 Saint-Petersburg, Russia.

2. At the XIII scientific-practical conference of young scientists and students with international participation, dedicated to the «Year of the Development of Tourism and Folk Crafts». April 27, 2018 Dushanbe. Tajikistan.

3. At the 56th Polish and 14th international scientific and practical conference of student scientific societies and doctors. Juvenes pro medicina. May 25-26, 2018 Lodz, Poland.

4. At the international conference «Fundamental research carried out by young researchers and doctoral students» KazNMU, Almaty. November 20-21, 2018.

**Publications.** The main results that were obtained during the dissertation research were published in 4 publications, of which:

- 3 articles published in journals recommended by the Committee for Quality Assurance in Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan;

- 1 article published in a journal indexed by Scopus and Thomson Reuters databases and having a percentile above 25% at the time of publication;

### **The structure and scope of the dissertation**

The dissertation work is presented on 122 pages of a computer text, consists of an introduction, 3 chapters: literature review, description of the material and research methods, own research results; discussions; conclusions; list of references from 170 sources. The work is illustrated with 32 figures and 34 tables.