Doctoral school of Medical Sciences

Manuscript
UDC: [616.613+616.617]-003.7-089.879-073.756.8(042.3)

BRADU Andrei

VALUE OF TOMOGRAPHIC DENSIOMETRY IN THE TREATMENT OF RENOURETERAL LITHIASIS BY EXTRACORPOREAL LITHOTRIPSY

321.22 – UROLOGY AND ANDROLOGY

Summary of the thesis of the Doctor of Medical Sciences

Chisinau, 2020

The research thesis was carried out within the Department of Urology and Surgical Nephrology, *Nicolae Testemitanu* PI State University of Medicine and Pharmacy, PMHCF Republican Clinical Hospital "Timofei Moșneaga", and the founding Consortium of the Doctoral School of Medical Sciences.

Scientific leader:
Ceban Emil,
Dr. habil., MD PhD, prof. ________________________________

Members of the steering committee:

Tănase Adrian,
MD PhD, prof. ________________________________

Bernic Jana,
MD PhD, prof. ________________________________

Pleșca Eduard,
MD PhD, assoc. prof. ________________________________

The thesis defense will take place on 01.07.2020, at 12.00, at *Nicolae Testemitanu* SUMPh, 165 Ștefan cel Mare şi Sfânt str., office 205, at the meeting of the Committee for public defense of the doctoral thesis, approved by the decision of the Scientific Council of the Consortium of 04.02.2020 (minutes no. 10).

Committee for public defense of the doctoral thesis:

Chairman:
Dumbrăveanu Ion
MD PhD, assoc. prof. ________________________________

Members :

Bernic Jana
MD PhD, prof. ________________________________

Jinga Viorel
MD PhD, prof. (Romania) ________________________________

Ceban Emil
Dr. habil., MD PhD, prof. ________________________________

Tănase Adrian
MD PhD, prof. ________________________________

Ghicavîi Vitalii
MD PhD, assoc. prof. ________________________________

Axenti Alin
MD PhD ________________________________

Author:
Bradu Andrei ________________________________

CONTENTS

LIST OF ABBREVIATIONS

EAU – European Association of Urology
AUA – American Urological Association
ESWL – extracorporeal shock wave lithotripsy
FDA – Food and Drug Agency
PMHCF – public medical health care facility
UTI – urinary tract infection
UPJ – Ureteropelvic junction
R L – renal lithiasis
RUL – renal ureteral lithiasis
PNL – percutaneous nephrolithotomy
VRR – voided renovesical radiography
KUB – plain abdominal radigraphy
CT – computed tomography
HU – Hounsfield units
IVU – intravenous urography
URS – ureteroscopy
USG – ultrasonography
IP SUMPh – *Nicolae Testemițanu* Public Institution State University of Medicine and Pharmacy
Stone free – absence of calculi

CONCEPTUAL LANDMARKS OF THE RESEARCH

Introduction. The results of treatment of renoureterial lithiasis by extracorporeal shock wave lithotripsy (ESWL) are determined by the knowledge of calculus density in Hounsfield units (HU) before ESWL, assessed by computed tomography (CT). Due to extremely high diagnostic sensitivity and specificity of CT in case of renouretal lithiasis, it is now also becoming a method of choice in selecting the treatment tactics of renouretal lithiasis. The modern literature in the field describes the concept of fragility and chemical composition of calculus with a major impact on assessing the effectiveness of treatment method. Thorough analysis of the publications in the field demonstrates the importance and impact of determining calculus density by CT, substantially increasing the "stone free" rate, minimizig the development of complications and avoiding unnecessary treatment procedures.

Data in the field of research problem. Urolithiasis is a disease which has been known since ancient times. Its prevalence in the general population varies between 2-3% worldwide [1, 12, 19], constantly increasing [1, 2]. In 2019 global multicenter epidemiological studies published data on urolithiasis incidence in Asia ranging from 1 to 5% of the population, as well as in Saudi Arabia, where there is the highest prevalence in the world, amounting to 20.1% [1, 2]. The average prevalence in Europe is 5-9%, while in Canada and the USA it amounts to 13-15% [19, 20]. The incidence of urolithiasis is about 3 times higher in men than in women, the ratio being 2.7:1 [3, 5]. In the Republic of Moldova there is also evidence of an increased incidence and prevalence of urolithiasis. Since 2005 to date it has ranked first in the structure of urologic diseases [3, 6, 7]. Untreated renoureteral lithiasis significantly increases the frequency of severe complications and is ranked third by the cause of death in the structure of urologic diseases [4, 6, 7]. Proper management involves different diagnostic methods for the early detection of disease as well as the use of modern methods of treatment of urolithiasis in accordance with national and international guidelines [10]. The application of CT densitometry facilitates the determination of the average density of calculus, predicting its fragility, and subsequently ESWL prognosis [10, 13]. The density of calculus is variable depending on its chemical composition [6, 8]. Thus, it is recommended to know calculus fragility before ESWL, in order to increase the efficiency of treatment by ESWL, as well as to reduce the number of ESWL sessions and implicitly the costs. Due to an ongoing scientific and technical progress, treatment of renoureteral lithiasis is at a new stage of development, which is due to a continuous modernization of endourologic treatment techniques and ESWL devices [5, 6, 21]. ESWL is a method of treatment popular among urologists, as it is less invasive in comparison with other endoscopic or classical surgical methods for renoureteral lithiasis treatment [8]. This method is a therapeutic technique for disintegration of renoureteral stones, being effective in complete treatment of RUL [7]. Since the introduction of ESWL as a treatment method in medical practice, negative and positive factors influencing the method have been analyzed in order to make it more effective [9]. The ESWL outcome depends on several factors, such as calculus size, localization, chemical composition, fragility, type of lithotripter, presence of urinary tract infection or obstruction [2]. When the concept of calculus fragility was introduced, the chemical composition became the main factor influencing ESWL effectiveness [12]. ESWL generates shock waves outside the human body which are focused on the calculus [2, 4]. As a result, calculi are disintegrated into tiny fragments, which subsequently are physiologically removed in urine through the urinary tract. The use of shock waves in the fragmentation of calculi is the method known to urologists since the 1950s, being initially used to fractionate calculi by direct contact. Extracorporeal shock waves can propagate with greater intensity, smaller energy loss, and minimal tissue damage or breakdown.

With the introduction of extracorporeal shock wave lithotripsy (ESWL) in 1980 by Chaussy [1], the method has become the treatment of choice for kidney stones smaller than 2 cm in diameter and ureteric stones up to 1.5 cm. The method is based on the disintegration of calculi by shock waves produced outside the body (extracorporeal), which penetrate the tissues without causing injury [2]. Due to the progress of minimally invasive methods, in 80 - 90% of patients with renoureteral lithiasis ESWL is indicated to treat the disease, in 8-10% endourological techniques are used (PNL, URS, RIRS) and only in 1-2% conventional surgery is performed [3].

The research purpose was to assess the role of CT and CT types, in order to establish the density of calculi in patients with renoureteral lithiasis, treated by ESWL, and to improve the diagnosis of disease, as well as to increase the efficiency of treatment and "stone-free" rate.

Research objectives

1. To thoroughly study the treatment of renoureteral lithiasis by ESWL.
2. To assess CT and CT phases in order to improve the diagnosis of patients with renoureteral calculi.
3. To determine the effectiveness of diagnosis and treatment of kidney stones and ureteric stones by ESWL.
4. To apply CT densitometry in assessing calculus density outcome in patients with renoureteral lithiasis.
5. To determine the indications for ESWL depending on renoureteral calculus density.
6. To study pre-and post-ESWL factors that influence the treatment outcome, as well as the increase of the "stone-free" rate in patients with RUL by applying CT densitometry of calculus.

Scientific novelty and originality

1. The research work represents a comprehensive study of the treatment outcome of renoureteral lithiasis by ESWL depending on calculus density (HU) assessed by CT, which has been carried out at the Department of Urology and Surgical Nephrology, *Nicolae Testemițanu* State University of Medicine and Pharmacy and the Clinic of Urology of PMHCF Republican Clinical Hospital *Timofei Moșneaga*.
2. It was demonstrated that assessment of calculus density by CT in HU is an important factor in determining the number of sessions necessary for renoureteral calculus disintegration in the treatment of renoureteral lithiasis by ESWL.
3. The post-ESWL „stone free" rate was also studied depending on calculus density assessed by CT.

Scientific problem solved in the thesis

- Assessment of CT densitometry of renoureteral lithiasis increases ESWL success, being directly proportional to the increase in "stone free" rate, prevention or decrease of complications after ESWL.
- CT examination is currently considered the standard imaging test for the diagnosis of renoureteral lithiasis, providing accurate information on stone size, localization and, most importantly, density (hardness), which is measured in Hounsfield units (HU).

Theoretical significance and applicative value of the research

- Approving methods of investigation and assessment of patients with renoureteral lithiasis.

- Optimizing the indications for treatment of renoureteral lithiasis by ESWL depending on tomographic density of calculus.
- The treatment tactics of renoureteral lithiasis have been studied and developed depending on calculus localization, duration of calculus persistence, calculus size and complications.
- The research demonstrated the importance of assessing calculus density order to establish precise indications for the treatment of renoureteral lithiasis by ESWL and to select an appropriate method.
- Based on the analysis of calculus density, ESWL effectiveness was argued.

On the results obtained, indications, contraindications and treatment algorithm of renoureteral lithiasis by ESWL were developed, depending on calculus density.

-
- The criteria elaborated and recommended by the author in order to determine calculus density by CT in patients with renoureteral lithiasis decrease the number of unnecessary ESWL sessions, clearly stratify indications, reduce the duration of exposure of the patient and doctor to X-rays, prevent complications that lead to renal function decline, having a significant economic impact.

Implementation of scientific results

The scientific results obtained have been applied in the educational process at the Department of Urology and Surgical Nephrology of *Nicolae Testemițanu* State University of Medicine and Pharmacy, in the teaching process of resident students and doctors, as well as in continuing medical education courses and clinical activity at the Department of Urology, Endourology and ESWL Unit of PMHCF RCH *"Timofei Moșneaga"* and Department of Urology of PMHCF MCH "*Sf. Treime"*.

Approval of research results

The research materials and results obtained in the doctoral thesis were presented at the following scientific forums: Conference with international participation held by the Urological Society of the Republic of Moldova (October), *Diagnosis, treatment and prophylaxis of urolithiasis* (Chișinău, October 2014); 6th Congress of Urology, Dialysis and Renal Transplantation of the Republic of Moldova with international participation (Chisinau, October 2015); 6th International Medical Congress for Students and Young Doctors *MedEspera* (Chisinau, May 2016); 7th International Medical Congress for Students and Young Doctors *MedEspera* (Chisinau, May 2018); XXXII Congress of the Romanian Association of Urology (Bucharest, Romania, June 2016); XXXIII Congress of the Romanian Association of Urology (Bucharest, Romania, June 2017); VII Congress of Urology, Dialysis and Renal Transplantation of the Republic of Moldova with international participation (Chisinau, June 2019); Annual scientific conferences held by *Nicolae Testemițanu* PI SUMPh (Chisinau, 2015, 2016, 2017, 2018, 2019).

The thesis was discussed, approved and recommended for defense at the joint meeting of the steering group members, the scientific leader and members of the Department of Urology and Surgical Nephrology of *Nicolae Testemiţanu* PI State University of Medicine and Pharmacy (minutes no. 7 of 27 December 2019) and at the meeting of the Scientific Specialized Seminar 321. General medicine; specialties, 321.13 *Surgery*; 321.14 *Pediatric Surgery*; 321.22 *Urology and Andrology* (Minutes no. 2 of 19 February 2020).

Contents of thesis compartments

The doctoral dissertation is set out on 125 pages of printed text, including 16 figures, 23 tables, 1 formula and 9 appendices. The thesis comprises an annotation in Romanian, Russian and English, an introduction, four chapters, general conclusions, practical recommendations, bibliography of 227 references. On the subject of the research thesis, 24 scientific papers were published, including 3 publications without coauthors and 2 publications in reviewed editions.

Keywords: extracorporeal shock wave lithotripsy, renoureteral lithiasis, calculus densitometry, computed tomography.

The doctoral thesis received the positive opinion of the Research Ethics Committee of *Nicolae Testemitanu* PI State University of Medicine and Pharmacy (Minutes no. 49/40 of 10 May 2016).

THESIS CONTENTS

The ***Introduction*** includes the theoretical aspects of the components analyzed in the research, the up-to-dateness of the topic addressed, the purpose and objectives of the study, the scientific novelty and originality of the obtained results, the theoretical and applicative significance of the thesis, the approval of the obtained results and the overview of thesis compartments.

1. TREATMENT OF RENOURETERAL LITHIASIS BY EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY

(literature review)

The research work contains literature data and recent information on renoureteral lithiasis: etiopathogenesis, theories of stone formation in the urinary system, current diagnosis and treatment methods of RUL by ESWL.

However, according to the literature, the success rate of renoureteral lithiasis treatment by ESWL is pointed out, as well as ESWL advantages and disadvantages, the occurrence and management of complications and patient's behavior after ESWL.The approaches found in the literature concerning the management of renoureteral lithiasis are considered within the systemic assessment of the human body, using a multimodal clinical approach.

Also, the necessary steps to be taken after making the diagnosis of renoureteral lithiasis are described, as well as the choice of treatment method and treatment customization following the necessary examination and tests, to minimize the risk of complications. Discussions about the importance of assessing stone density by CT entail a particular therapeutic conduct in order to evaluate the effectiveness of treatment of renoureteral lithiasis by ESWL.

The European treatment guidelines of RUL contain recommendations on treatment protocol of renoureteral lithiasis by ESWL, involving key-factors such as calculus density and localization, the morphofunctional status of the urinary system, as well as the number of ESWL sessions performed. Data confirm that after the first ESWL session the success rate reaches 65-70%, after the second session the success rate amounts to 85%, while after the third session it accounts for 95%.

2. RESEARCH MATERIAL AND METHODS

2.1. Statutory-clinical characteristics of the study group

The research work includes the description of the research methodology and methods, as well the information on study groups and the method of statistical evaluation of the obtained results. The research was carried out on a group of 130 patients, in order to confirm the research hypothesis.

All the subjects included in the study were selected from the clinical setting of the

Department of Urology and Surgical Nephrology, *Nicolae Testemiţanu* State University of Medicine and Pharmacy, the Republican Clinical Hospital. There were 130 patients subjected to treatment by ESWL, accounting for 100%, between May 10, 2016 and December 30, 2018.

2.2. Methods of clinical and paraclinical examination of patients

All the data obtained in the study of clinical evolution of renoureteral lithiasis in the patients enrolled in the research formed the basis of the study of ESWL effectiveness and ESWL implementation. Also, the data collected served as a basis for the determination of particularities of diagnostic imaging methods of renal lithiasis, with the subsequent calculus stratification according to tomographic calculus density. This group of patients also included the experimental subgroup and the group of patients who developed some complications and who were subjected to other therapeutic methods, which facilitated the fast resolution of complications.

Group I: Patients subjected to plain CT, angio or urogaphic, with the determination of renoureteral calculus density treated by ESWL. Patients with calculus density >1200 HU were not included in the research, other treatment methods such as ureteroscopy with intracorporeal lithotripsy or intrarenal retrograde surgery being performed. Only patients with calculus density from 200 to 1200 HU determined by CT were included in the experimental group for ESWL.

Group II: Patients with renoureteral lithiasis confirmed by intravenous urography, general radiography (plain film radiography), ultrasound. The tomographic density of calculus was not known.

To achieve the research purpose and objectives, patients were randomly selected and CT densitometry was assessed. The number of patients required for research was calculated by the following formula:

$$n = \frac{1}{(1-f)} \times \frac{2(Z_\alpha + Z_\beta)^2 xP(1-P)}{(P_o - P_1)^2}, \qquad (1)$$

where:

P_0 – the proportion of patients subjected to ESWL without CT, undergoing only intravenous urography, general radiography, USG and treated by ESWL. According to bibliographic data, the success rate of calculus disintegration is different and constitutes, on average, 50.0% (P_0 = 0.50).

P_1 – patients subjected to general CT, with the determination of renoureteral calculus density and treated by ESWL.

The rate of calculus disintegration can reach 70-90%, on average, 80.0% of cases (P_1 = 0.80):

$P = (P_0 + P_1)/2 = 0{,}65$.

$Z\alpha$ –table value: when the statistical significance is 95.0%, then coefficient $Z\alpha = 1.96$.

Z_β – table value: when the statistical power of comparison is 90.0%, then coefficient $Z_\beta = 1.28$.

f – the proportion of subjects expected to leave the study by different reasons than the investigated effect q = 1 / (1-f), f = 10.0% (0.1).

By introducing data into the formula, it was obtained:

$$n = \frac{1}{(1-0.1)} \times \frac{2(1.96+1.28)^2 x0.65x0.35}{(0.50-0.80)^2} = 59.$$

Therefore, experimental group L_I included 60 patients with CT (plain), or angio-urographic CT, with the determination of renoureteral calculus density, treated by ESWL and the control group L_{II} comprising 70 patients not subjected to CT, renoureteral lithiasis being diagnosed by intravenous urography, general radiography, ultrasound, treated by ESWL. Prior to enrollment in the study, the patients` informed consent was obtained.

The subjects were selected according to inclusion and exclusion criteria. The patients were subjected to clinical-anamnestic and paraclinical examination based on the approved study protocol. The study was approved in accordance with the ethical requirements and received a favorable opinion of the Research Ethics Committee of *Nicolae Testemitanu* PI SUMPh, no. 49/40 of May 10, 2016.

2.3. Methods of statistical analysis of obtained data

Statistical analysis of the results obtained was carried out by means of specialized computer programs using the statistical program SPSS-10 IBM Statistics for Windows, 20 Microsoft Excel 2010, as well as descriptive, variation and correlation analyses. The statistical tests used were as follows: Student`s t-test, ANOVA, $\chi2$ - Pearson test, relative risk determination. The qualitative parameters were compared by $\chi2$ - Pearson and Fisher`s method, in case of a small number of parameters.

The quantitative parameters were expressed by the mean value and standard error value. The Student`s t-test was used to estimate the statistical differences between the average values of the wo groups. Dispersion analysis was used to perform the equality test of three and more groups of parameters. The linear Pearson correlation coefficient (r) was applied to assess the correlation between some phenomena studied. Value $p < 0.05$ was considered statistically significant.

3. RESEARCH RESULTS

The analysis of effective diagnosis and treatment methods of RUL by ESWL is widely reflected, including assessment, by comparison, of the data obtained in patients` interviewing. The study groups were made according to similar criteria of inclusion and subjects enrolled in the study matched by age, research methods and treatment procedures.

The majority of patients subjected to ESWL were treated in an outpatient setting. Patients in a serious condition were hospitalized, including subjects with a solitary kidney, either congenitally or surgically, were also admitted to the hospital. The group of patients included in the study had RUL with different localization or fragments remaining after minimally invasive procedures.

Also, before subjecting patients to treatment of renoureteral lithiasis by ESWL, it is important to examine patients by clinical and paraclinical methods, to assess the tomographic density of calculus, and to receive information on kidney function and morphofunctional condition of renal parenchyma.

Before ESWL, the patients included in the study were subjected to intravenous urography or computed tomography to assess the density of calculus. The radiological investigations were indispensable in order to reduce the risk of complications, as well as to increase the safety of out-patient treatment of ESWL.

To relieve pain, non-steroidal anti-inflammatory drugs were administered to all patients included in the research. Analgesics were administered intravenously. The majority of patients enrolled in the research were subjected to ESWL which was performed under out-patient conditions. Patients requiring hospitalization for monitoring, in order to reduce or prevent the development of complications after ESWL, were hospitalized in the Department of Urology.

Distribution of patients included in the study by age and study group is depicted in table 1.

The study included 130 patients with the diagnosis of renoureteral lithiasis, treated by ESWL, the density of calculus being assessed in HU. Of these, 60 patients made up the experimental group, who were subjected to standardized laboratory and imaging investigations. The ”stone free” rate was assessed as a criterion of resolving the treated case. CT was performed to determine the density of calculi.

Table 1. **Distribution of patients by age and study group**

Age	Experimental group (n=60)		Control group (n=70)		p
	abs.	%	abs.	%	
18-30 years	10	16,7 ÎI 95% [7,2-26,1]	7	10,0 ÎI 95% [3,0-17,0]	χ^2=1,932, gl=3, p>0,05
31-40 years	6	10,0 ÎI 95% [2,4-17,6]	11	15,7 ÎI 95% [7,2-24,2]	
41-59 years	23	38,3 ÎI 95% [26,0-50,6]	28	40,0 ÎI 95% [28,5-1,5]	
over 60	21	35,0 ÎI 95% [22,9-47,1]	24	34,3 ÎI 95% [23,2- 5,4]	

Table 2. **Distribution of patients included in the study by anatomical calculus localization**

Calculus localization	Experimental group, (n=60)		Control group, (n=70)		p
	abs.	%	abs.	%	
Renal pelvis	22	36,7 ÎI 95% [24,5-8,9]	24	34,3 ÎI 95% [23,2-5,4]	χ^2=1,932, gl=3, p>0,05
Upper ur.	16	26,7 ÎI 95% [15,5-37,9]	22	31,4 ÎI 95% [20,6- 2,3]	
Lower ur.	22	36,7 ÎI 95% [24,5-48,9]	20	28,6 ÎI 95% [18,0- 9,2]	

The patients from both groups were distributed according to the criterion of calculus localization. It is important to know calculus localization before the patient is subjected to ESWL because it is necessary to apply the correct position, either dorsal or ventral decubitus, to facilitate accurate penetration of shock waves.

Table 3. **Distribution of patients by calculus size and study group**

Calculus size	**Experimental group, (n=60)**		**Control group, (n=70)**		**p**
	abs.	**%**	**abs.**	**%**	
0,3-0,6 cm	8	13,3 CI 95% [4,7-21,9]	9	12,9 CI 95% [5,0-20,7]	χ^2=0,028, gl=3, p>0,05
0,7-0,9 cm	31	51,7 CI 95% [39,0-64,3]	37	52,9 CI 95% [41,2-64,6]	
1,0-1,5 cm	20	33,3 CI 95% [21,4-45,3]	23	32,9 CI 95% [21,9-43,9]	
1,6-2,0 cm	1	1,7 CI 95% [1,6-4,9]	1	1,4 CI 95% [1,4-4,2]	

In order to correctly stratify the indications for ESWL, the patients from both groups were distributed according to the classification of renoureteral calculi by size.

Table 3 shows the predominance of small and medium-sized calculi correlated with treatment indications. According to national and international protocols the maximum diameter of renal calculi is 2 cm, while the maximum diameter of ureteral calculi is 1.5 cm.

The duration of calculus persistence in the renoureteral system is an important criterion in gaining relevant differential comparative data on calculi and appropriate results in each group (figure 1).

It was demonstrated that the duration of calculus persistence directly and proportionally influences its density. Calculus hardness in terms of density is an important factor that determines calculus fragmentation following ESWL. As a result, the duration of calculus persistence in the urinary system directly influences treatment outcome.

In lithiasis, calculus increases in size and its hardeness increases as well. The overall duration of calculus persistence in patients included in the study was 6.2 ± 0.59 months, a difference between the experimental group (7.5 ± 0.96 months) and control group (5,1±0,69 months) being revealed (F=4,478, p=0,036).

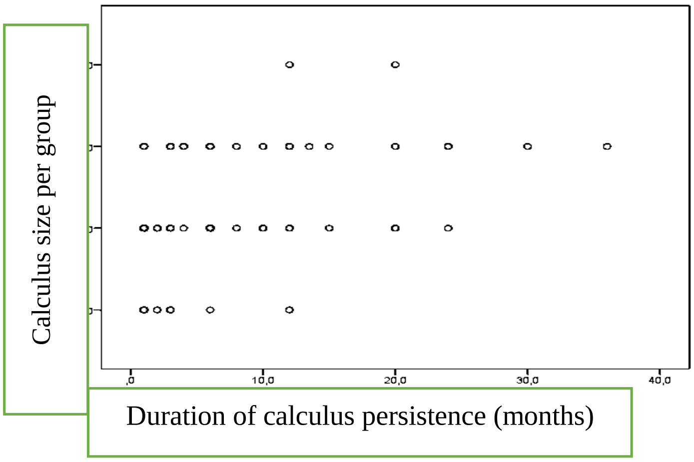

Figure 1**. Correlogram of calculus size and overall duration of calculus persistence in patients included in the study**

The analysis of calculus size and the overall duration of calculus persistence revealed a statistically significant direct mean correlation (figure 1).

Table 4. **Distribution of patients from the experimental group by sex and calculus density**

Sex	**0-300 HU n=12**	**300-600 HU n=12**	**600-900 HU n=22**	**900-1200 HU n=14**	**P**
Women	8	7	9	4	χ^2=4,720, gl=3, p>0,05
Men	4	5	13	10	

The analysis of patients` age in the experimental group depending on calculus density showed that the highest density 900-1200 HU was revealed in elderly patients - 57.0 ± 3.67 years, followed by patients aged - 55.7 ± 4.41 years with density 300-600 HU. The analysis revealed a statistically significant difference (F = 2,785, p = 0.049), (figure 2).

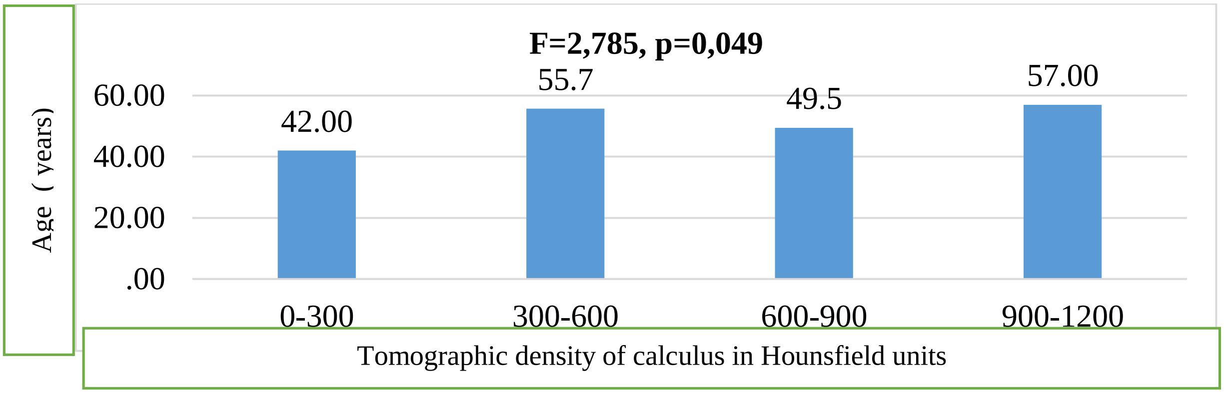

Figure 2. **Average age of patients from the experimental group by calculus density (years)**

The correlation between the presence or absence of hydronephrosis in the experimental group was studied depending on calculus density 600-900 HU - 19 subjects out of 22, most of them having ureterohydronephrosis, grade 2. In other groups of calculus density, the distribution of patients by the presence and degree of disease is relatively uniform, with no statistical difference (table 5).

It is important to assess ureterohydronephrosis grade in order to evaluate the morphofunctional status of the renal parenchyma, to assess the possibility of the kidney to expel calculus fragments following ESWL. The possibility of kidneys with hydronephrosis gr.3 to expel calculus fragments after ESWL is comparatively smaller than the possibility of expulsion in patients without hydronephrosis. The anatomical localization of calculi depending on their density did not show any statistically significant differences, calculi being distributed relatively uniformly (table 5).

Table 5. **Distribution of patients from the experimental group depending on ureterohydronephrosis and calculus density (HU)**

Ureterohydronephrosis grade	**0-300 HU n=12**	**300-600 HU n=12**	**600-900 HU n=22**	**900-1200 HU n=14**	**P**
Absence of ureterohydronephrosis	3	4	3	7	χ^2=10,836, gl=9, p>0,05
Gr. 1	3	3	6	4	
Gr. 2	3	1	8	3	
Gr. 3	3	4	5	0	

Table 6. **Distribution of patients from the experimental group depending on calculus localization and density**

Calculus localization	**0-300 HU n=12**	**300-600 HU n=12**	**600-900 HU n=22**	**900-1200 HU n=14**	**P**
Renal pelvis	2	6	6	8	χ^2=9,096, gl=6, p>0,05
Upper ureter	5	2	10	5	
Lower ureter	5	4	6	1	

Analysis of data on calculus localization and tomographic calculus density revealed the predominance of pelvic lithiasis in 22 patients. Of them, 8 patients had calculus hardness between 900 -1200 HU, followed by calculi located in the upper and lower ureters. In terms of calculus localization depending on laterality (right, left), there was no statistically significant difference ($\chi 2$ = 1,991, gl = 3, p> 0.05).

The mean number of calculi by density was higher in groups with density 0-300 and 300-600 (1.2 ± 0.39), but with no statistically significant difference (figure 3).

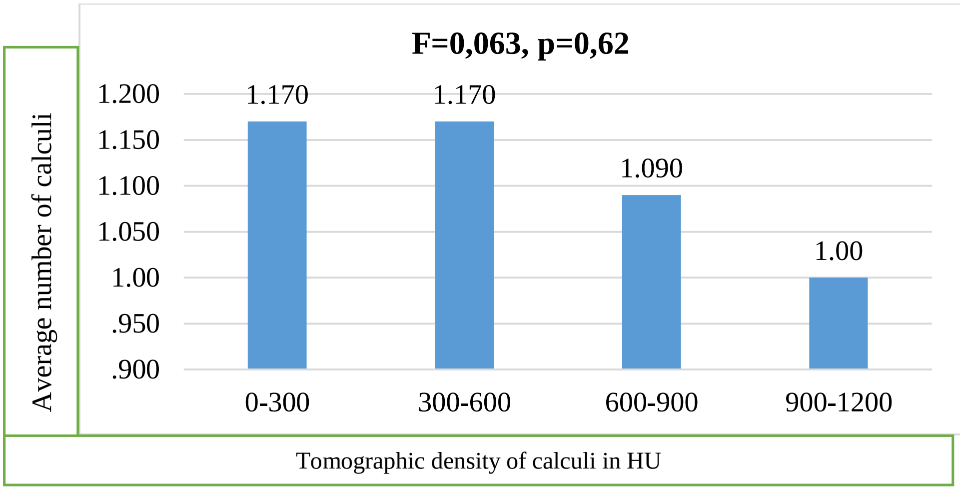

Figure 3. **Average number of calculi in patients from the experimental group by calculus density**

The size of most calculi in the experimental group accounted for 0.7-0.9, being revealed in patients with calculus density 600-900 HU. There was no statistically significant difference between groups (table 7).

The duration of calculus persistence is a criterion that can directly influence calculus density, being also confirmed by direct correlation r_{xy} = 0.310. Thus, the longest duration was recorded in the group of patients with calculus density 900-1200 HU - 12.1 ± 2.42 months, followed by the group of calculus density 600-900 HU - 7.0 ± 1.61 months. The duration of calculus persistence in groups 0-300HU and 300-600HU was practically identical: 5.4 ± 1.6 months and 5.2 ± 1.34 months, respectively. These data show a statistically significant difference (F = 2,774, p = 0.049), (figure 4).

Table 7. Distribution of patients from the experimental group by calculus size and density (HU)

Calculus size	**0-300 HU n=12**	**300-600 HU n=12**	**600-900 HU n=22**	**900-1200 HU n=14**	**p**
0,3-0,6	3	0	5	0	χ^2=13,847, gl=9, p>0,05
0,7-0,9	5	7	13	6	
1,0-1,5	4	5	3	8	
1,6-2,0	0	0	1	0	

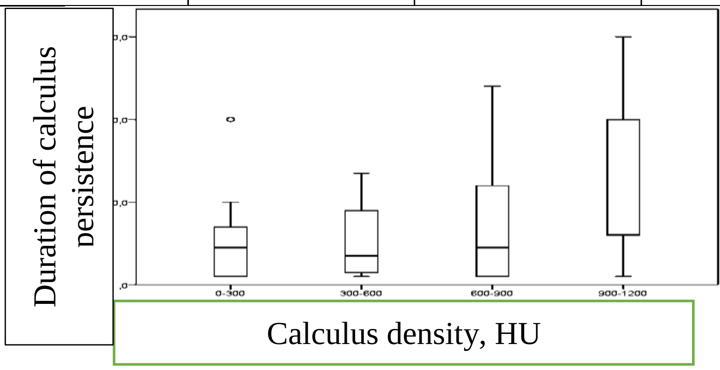

Figure 4. **Mean duration of calculus persistence in the experimental group by calculus density (abs.)**

Radiologically positive calculus opacity was found in 52 (86.7%) patients from the experimental group, being uniformly distributed according to the group of calculus density, radiologically negative in 8 (13,3%) patients, respectively. These data confirm the predominance of radiologically positive lithiasis.

Blood test (complete blood count) was the first clinical examination performed in patients in the experimental group. Absolute values of blood count (red blood cell count, hemoglobin count, white blood cell count, non-segmented neutrophil count) did not show any statistically significant difference by the group of calculus density (table 8).

Table 8. **Indices of hemogram by calculus density**

Blood test parameters	**0-300HU Mean±SE**	**300-600HU Mean±SE**	**600-900HU Mean±SE**	**900-1200HU Mean±SE**	**p**
No. of erythrocytes (x 10^{12}/l)	4,3±0,13	4,4±0,23	4,6±0,14	4,9±0,14	F=2,289, p=0,088
Hemoglobin (g/l)	132,2±2,63	129,5±4,46	134,7±3,06	142,9±3,06	F=2,612, p=0,060
No. of leucocytes (x 10^9/l)	6,2±0,31	6,5±0,43	6,8±0,22	7,0±0,27	F=1,347, p=0,269
Segmented neutrophils (%)	3,1±0,14	3,3±0,47	2,9±0,24	3,9±0,50	F=1,539, p=0,215

The obtained results showed that, approximately in half of the patients from the experimental group, the urine reaction was neutral - 34 (56.7%, CI 95% [44,1-69,2]) cases. Urine acidity reaction was found in 15 25.0%, CI 95% [14.0-36.0]) cases. There was no statistically significant difference between groups with different calculus density (table 9).

Table 9. **Distribution of patients** included **in the research by urine reaction**

Urine reaction (urine pH)	Experimental group, (n=60)		Control group, (n=70)		p
	abs.	%	abs.	%	
Acidic pH 5 – 6. 8	15	25,0 CI 95% [14,0-36,0]	15	21,4 CI 95% [11,8-31,0]	χ^2=2,370 , gl=2, p>0,05
Basic pH 7.5- 9.0	11	18,3 CI 95% [8,5-28,1]	21	30,0 CI 95% [19,3-40,7]	
Neutral pH 6.9 – 7.4	34	56,7 CI 95% [44,1-69,2]	34	48,6 CI 95% [36,9-60,3]	

All the patients in the experimental group were subjected to ESWL with *Modulith SLK Stortz* lithotripter. The number of ESWL sessions differed depending on calculus density, a high direct correlation being observed: r_{xy} = 0.65. Thus, patients in the group with calculus density 0-300 HU required the smallest number of ESWL sessions - 1.3 ± 0.14, patients in the group with calculus density 900-1200 HU required most ESWL sessions – 2,7±0,13 (table 10).

Table 10. **Distribution of patients from the experimental group by the number of ESWL sessions and calculus density**

No. of ESWL sessions	**0-300 HU n=12**	**300-600 HU n=12**	**600-900 HU n=22**	**900-1200 HU n=14**	**p**
Mean±ES	1,3±0,14	1,8±0,17	2,0±0,10	2,7±0,13	F=16,942, p=0,000
Minimum	1	1	1	2	-
Maximum	2	3	3	3	-

Analysis of the results obtained revealed a similar lawfulness both in case of the number of ESWL sessions and the number of impulses applied. The correlation between the density of calculus and the number of impulses applied is r_{xy} = 0.65. The lowest number of impulses – 5333.3 ± 568.53 was applied to patients in the group with calculus density 0-300 HU, while the highest number of impulses – 10857,1±501,1760 was applied to the group with calculus density 900-1200 HU (table 11).

Table 11. **Distribution of patients from the experimental group by the number of impulses per ESWL session and calculus density**

No. of impulses per session	**0-300 HU n=12**	**300-600 HU n=12**	**600-900 HU n=22**	**900-1200 HU n=14**	**p**
Mean±ES	5333,33±568,53	7333,3±666,67	7818,2±414,23	10857,1±501,18	F=16,942, p=0,000
Minimum	4000	4000	8000	4000	-
Maximum	12000	12000	12000	12000	-

Analysis of the correlation between the total number of impulses of three ESWL sessions and calculus density found a statistically significant correlation between the need for a higher number of impulses and a higher number of ESWL sessions, respectively, in case of calculi of an increased hardness.

The frequency of impulses in all patients including the experimental group was equal to 2.0 Hz. The impulse intensity did not show any statistically significant difference (F = 2,100, p = 0,111), (figure 5).

Although calculus size greatly influences ESWL outcome, calculus density has a much greater impact on the outcome than its size (p > 0.05).

The analysis of calculus size and overall duration of calculus persistence showed a mean direct correlation of calculus persistence and hardness $r_{xy}=0.436$ (figure 6)

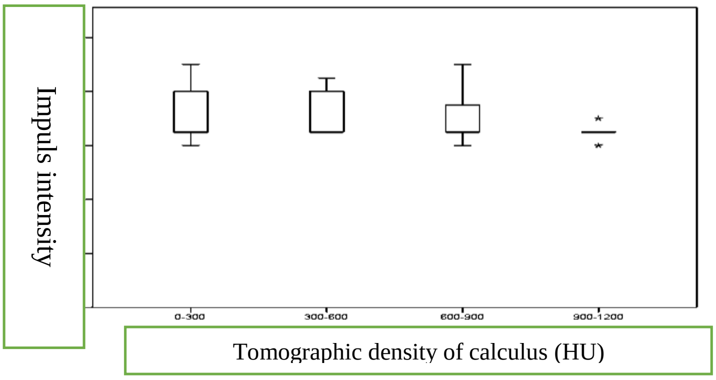

Figure 5. **Average intensity of impulses applied in the experimental group depending on calculus density (abs.)**

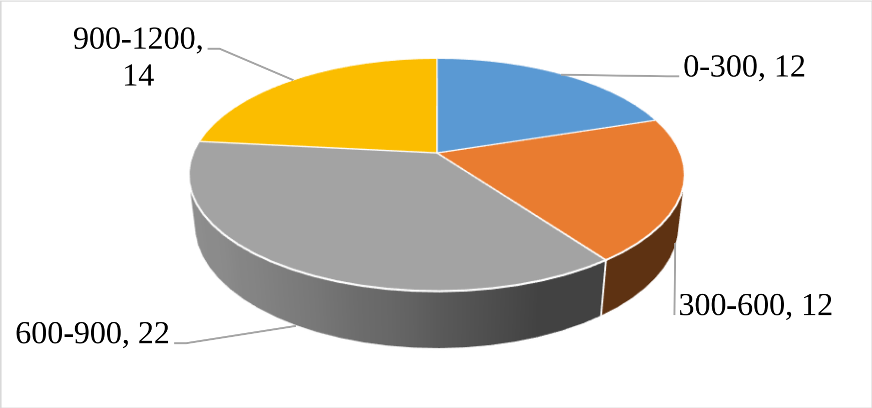

Figure 6. **Distribution of patients from the experimental group by calculus density, assessed by tomographic densitometry (%)**

The analysis of absolute values of calculus density revealed the following results: minimum calculus density - 199 HU, maximum calculus density - 1200 HU, and mean value = 657,0 HU ±39,49.

The chemical composition and density of calculus were an essential factor in correct stratification of patients undergoing ESWL, being a determining factor of the significant decrease in complications after ESWL, thus subsequently increasing the treatment success.

Table 12. **Calculus density by chemical structure**

Chemical structure of calculus	No.60	Percentage ratio	Density (HU)	p
Calcium oxalate (monohydrate and dihydrate)	32	58.33%	1091.8±93 HU	(p<0.001)
Uric acid	14	23.33%	396±71 HU	(p<0.001)
Magnesium-ammonium-phosphate	8	13.33%	605.7±71.8 HU	(p<0.001)
Cystine	3	5%	737.4±46.4 HU	(p<0.001)
Total	60	100%		

The data presented in the table highlight the predominance of calcium oxalate stones - 32/60 (58,33%) patients, with an average density 1091.8±93 HU (p <0.001), followed by uric acid stones - 14/60 (23.33%) patients, density 396 ± 71 HU (p <0.001). Magnesium-ammonium-phosphate stones were found in 8/60 (13.33%) patients, and 605.7 ± 71.8 HU (p <0.001), respectively, while cystine stones in 3/60 (5%) patients with density 737.4 ± 46.4 HU (p <0.001), respectively.

There was a direct linear correlation between the density in HU and the number of ESWL sessions required for calculus fragmentation. The fragmentation of calculus in a single ESWL session accounted for – 396±71 HU, 2 sessions - 737 ± 46 HU, 3 sessions - 1091 ± 226 HU, more than 3 sessions – 1134 ± 136 HU. High density calculi required a large number of ESWL sessions, otherwise it would not be possible to fragment calculi by ESWL.

As there are no medical procedures with a high degree of absolute safety, some post-ESWL complications were recorded in the research: kidney colic - 90.0% in the experimental group, and 95.7% in the control group, respectively (93,1%, CI 95% [88,7-97,4]), hematuria - 96.7% in the experimental group, 100.0%, respectively, in the control group (98,5%, CI 95% [96,3-100,6]), residual fragments – 51.7% in the experimental group, 54.3% in the control group (53,1%, CI 95% [44,5-61,7]) cases, steinstrasse (11.7%, experimental group, 2.9% control group, CI 95% [2.6-11. 3]) cases.

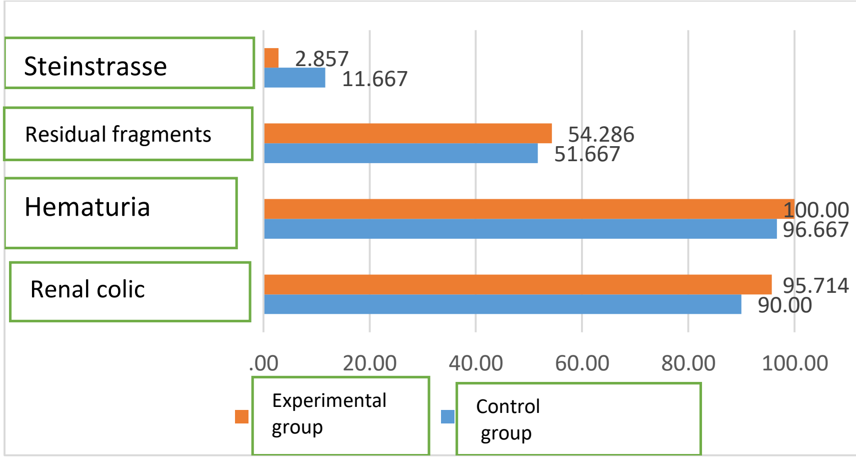

Figure 7. **Presence of post-ESWL complications in patients included in the research (%)**

The complications occurred in relatively equal proportions in patients of both groups, a statistically significant difference being found in steinstrasse (χ^2=3,891, gl=1, p<0,05) (figure 7).

The frequency of complications in the experimental group was studied, depending on the tomographic density of calculus in HU. Presented in descending order, the following complications were recorded: renal colic, hematuria, residual fragments, steinstrasse (table 13).

Table 13. **Distribution of patients from the experimental group by post-ESWL complications and calculus density in HU**

Post-ESWL complications	**0-300 HU n=12**	**300-600 HU n=12**	**600-900 HU n=22**	**900-1200 HU n=14**	**p**
Renal colic	10	10	20	14	χ^2=2,761, gl=3, p>0,05
Hematuria	10	12	22	14	χ^2=8,276, gl=3, p>0,05
Remaining fragments	3	6	13	9	χ^2=4,809, gl=3, p>0,05
Steinstrasse	1	2	0	4	χ^2=7,208, gl=3, p>0,05

The study showed a direct correlation of the frequency of post-ESWL complications, depending on the tomographic density of calculus. A direct correlation in the frequency of complications was observed, being directly proportional to the increase of tomographic density of calculus.

Following ESWL, a complete kidney recovery was revealed in 54 (90.0%, CI 95% [82.4-97,6]) patients from the experimental group. In the group with calculus density 0-300 HU, all the 12 patients recovered. The highest rate of non-recovery was recorded in the group of patients with calculus density 900-1200 HU – 3 out of 12 patients ($\chi2$ = 2.761, gl = 3, p> 0.05).

Also, the degree of failure increased along with calculus density growth, the highest share being recorded in the group with calculus density 900-1200 HU, with no statistically significant difference ($\chi2$=6,199, gl=3, p>0,05). Patients who developed complications were monitored until the resolution of complications - spontaneous resolution of hematuria, renal colic management by spasmolitics and anti-inflammatory drugs, residual calculus fragments and steinstrasse - repeated ESWL sessions, drug therapy, or stent placement by ureteroscopy (table 13).

It is essential to carry out a thorough assessment of patients in order to identify different complications and to correctly monitor these patients, as well as to apply invasive treatment methods such as ureteric stenting and repeated ESWL; antibiotic therapy, being justified as beneficial measures in preventing of complications and decreased renal function.

Table 14. **Distribution of patients from the experimental group by resolution of renoureteral lithiasis and calculus density (HU)**

Resolution	**0-300 HU n=12**	**300-600 HU n=12**	**600-900 HU n=22**	**900-1200 HU n=14**	**p**
Complete resolution	12	10	21	11	χ^2=4,685, gl=3, p>0,05
Failure	0	0	1	2	χ^2=6,199, gl=3, p>0,05

Clinical resolving of renoureteral lithiasis by ESWL in patients included in the study, we can say that 89 (68,5%, CI 95% [60,5-76,4]) recovered completely, of them 57 (90,0%, CI 95% [38,3-61,7]) of the experimental group and only half – 35 patients (50,0%, CI 95% [38,3-61,7]) - of the control group. There was a statistically significant difference between the studied groups (χ^2=23,941, gl=1, p>0,001).

However, treatment failure was found in 17 (7.64%, CI 95%) patients included in the study. Of them, there were 5 patients (8,3%, CI 95% [8,5-28,1]) from the experimental group and 12 patients (17.14%, CI 95%) from the control group, a statistically significant difference (χ^2=16,534, gl=1, p>0,001) being found.

4. SYNTHESIS OF OBTAINED RESULTS

The comparison between the research results and literature data was carried out. However, the research data provided relevant information on achieving great success in the treatment of renoureteral lithiasis by ESWL. According to literature data, the combination of ESWL with the assessment of calculus density by CT is currently considered the most efficient and least invasive method, being the first line treatment of renoureteral lithiasis.

ESWL, as a method of treatment depending on the tomographic density of calculus, is a method of choice of RUL treatment, with minimal complications and high "stone free " rates.

The major and significant importance of the clinical study was the assessment of calculus density by CT in HU. CT with densitometry was used as the main criterion to complete the study groups. Thus, the experimental group comprised four groups of calculus density 300 HU. The largest share of calculus density accounted for 600-900 HU – 22 cases (36,7%, CI 95% [24,5-48,9]), other groups of calculus density were distributed uniformly.

The analysis of absolute values of calculus density showed the following results: minimum density - 199 HU, maximum density - 1200 HU, mean value - 657 HU ±39,49. Perekalina, A., *et al.* advocate the application of ESWL only to patients with renoureteral lithiasis confirmed by CT with the compulsory assessment of calculus density, the maximum calculus density being 1200 HU [22].

A variety of factors were studied in the 130 patients included in the study, directly or indirectly influencing ESWL outcomes. There were differences between ”stone-free” rates after ESWL depending on patient`s age and comorbidity, disease duration, heredo-collateral history, presence or absence of urinary tract infection, position, calculus size and chemical structure. However, the highest ”stone free” rate was reported in young patients.

History of renoureteral lithiasis, ESWL sessions, and urinary tract infections are factors that significantly diminish the ”stone free” rate [6, 8, 9]. In all patients included in the study, the rate of calculus fragmentation after the first ESWL session constituted 67%. After the first session the majority of calculi were resolved. In 23% of patients, two ESWL sessions were necessary, an increased ”stone free” rate of 86% being recorded. About 10% of patients required three ESWL sessions, which resulted in a ”stone free” rate increase up to 95%.

There was a series of factors directly involved in the decrease of post ESWL success rate, namely, calculus size, localization, number of calculi, the state of the pelvicalyceal system, the absence or presence of congenital anomalies. In calculi ≤10 mm, the success rate constituted 90%, while in calculi >10 mm it amounted to 70% ($p<0,05$). In terms of calculus localization, the success rate was 87.3% in calculi in the renal pelvis, 88.5% in calculi in the upper calyx and 69.5% in calculi in the lower calyx ($p<0.05$). In terms of the number of calculi, in 1 calculus the success rate constituted 78.3%, in 2 or more calculi it was 62.8% ($p <0.001$). With regard to the state of the pelvicalyceal system, in patients with normal kidneys the success rate accounted for 83%, in kidneys with obstruction it was 76% ($p<0.05$). In the absence or presence of congenital anomalies, the success rate decreased from 79%, in calculi located in kidneys without congenital anomalies, up to 54%, in kidneys with anomalies ($p<0,03$).

Currently, the data published by renowned authors in the field of ESWL are focused on minimizing adverse effects and maximizing "stone-free" rates. Shah N. S. et al. published recommendations on ESWL importance: in calculi ≤ 1 cm, the success rate is 86%, compared to calculi > 1 cm in which the success rate is up to 63%, with statistically significant values. Qattan M. M. et al. published the results on ESWL success rate of 64% in calculi up to 1.5 cm after three ESWL sessions [15].

Matas A. A. et al. described "stone free" rates up to 95% after three ESWL sessions [16]. The research showed “stone free” rates up to 96% after three ESWL sessions in subjects in whom calculus density was known, compared to 76% of “stone free” rates in subjects with unknown calculus density, with a significant increase of both immediate and delayed complications.

According to literature data, auxiliary procedures are commonly necessary after ESWL, compared with PNL and retrograde intrarenal surgery (21,9%, 5,7% and 8,7%, respectively, $p<0,001$). This is due to minor complications, statistically significant more common in patients treated by pyelolithotomy (36 subjects, 16.6%), compared to those subjected to PNL (1 subject, 1,3%; $p<0,001$) and patients treated by ESWL (0%; $p<0,001$). The frequency of major complications was similar in all three study groups: 6.0% in patients treated by pyelolithotomy, 10.1% in patients treated by PNL, and 5.5% in patients subjected to ESWL [6].

ESWL is used worldwide as the first-line method of treatment of urinary calculi, being the least invasive (but not without complications) and covering 80-90% of indications for renoureteral lithiasis treatment [2, 4].

GENERAL CONCLUSIONS

1. Currently, ESWL is the method of choice in the treatment of renoureteral lithiasis, used as the first line treatment of kidney stones up to 2 cm and ureteric stones up to 1.5 cm in about 70 - 80% of the overall number of patients.
2. Computed tomography (native, angiographic and urographic phases with three-dimensional reconstruction) helps physicians make a correct diagnosis and predicts the type of calculus by the chemical structure of both radiopaque and radiotransparent calculi.

The sensitivity of CT reached 100%, which was also confirmed in the experimental group, where the rate of calculus detection was 100% of the total number of 60 patients.

3. The use of CT densitometry before ESWL determines the average calculus density, which can predict calculus fragility, consequently, the treatment outcome. This helps in planning alternative treatment in patients with a likely unsatisfactory outcome (increased hardness > 1200HU) and increase in ESWL efficiency, reducing the cost of treatment and avoiding unnecessary procedures.
4. Computed tomography along with assessment of calculus density in the experimental group increased the ,,stone free,, rate up to 96%, $p<0,05$ (cumulative in all subgroups, after three ESWL sessions) and significantly decreased complications, compared to the control group, where the ,,stone free,, rate constituted 76%, $p<0,05$, also significantly increased both immediate and late complications in this group of patients.
5. Assessment of calculus density by CT diminished significantly the risk of complications up to 12%, ($p <0.001$), as well as major complications up to 7% ($p<0,05$), compared to the control group. The occurrence of complications was directly related to correct indications before ESWL, being statistically significant.
6. The presence of concomitant diseases or cormobidities, the morphofunctional state of the renal parenchyma, the presence of urethrohydronephrosis, urine pH variations, the chemical structure of calculus, and the presence of development abnormalities of the urinary system decreased the proportion of ESWL success rate by up to 12% ($p <0.05$) in the experimental group and up to 17% ($p <0.05$) in the control group.

PRACTICAL RECOMMENDATIONS

1. In order to recommend the treatment by ESWL for a patient with renoureteral lithiasis, at the level of primary medicine or specialized outpatient medicine at the district level (urologist) it is necessary to perform clinical, paraclinical and imaging investigations for the assessment of the diagnosis of renoureteral lithiasis, stone location, and evaluation of morphological and functional state of the urinary system, evaluation of the permeability of the urinary tract. Mandatory CT scan with assessment of the density of the stone is the main method of diagnosis of renoureteral lithiasis that allows the establishment of indications for treatment by ESWL.
2. At the level of specialized medicine, secondary or tertiary urology departments shall establish the indications for the treatment of renoureteral lithiasis depending on the tomographic density of the stone, as well as its dimensions (renal lithiasis up to 20 mm and ureteral lithiasis up to at 15 mm, without obstruction of the lower distal pathways of calculus), therefore lithiasis with a tomographic density of up to 1200 HU, will be subjected to first-line treatment by ESWL, also at the level of secondary or tertiary urologist will be referred for treatment by ESWL and patients

who have absolute indications for laborious operations, with an increased risk of developing serious side effects, increased risk of anesthesia.

3. At the level of primary medicine or specialized medicine of all levels for infectious lithiasis, until the ESWL is recommended the treatment of urinary tract infection should be performed before ESWL depending on urine culture results. Thus, ESWL should be used only after urine sterilization.
   Prophylaxis with antibiotics is not justified without definite risk factors, such as a positive urine culture before ESWL, JJ stent or nephrostomy, history of infectious calculi and recurrent urinary tract infections.

.

REFERENCES

1. Bradu, A. Rolul litotritiei extracorporale cu unde de șoc în tratamentul litiazei renoureterale. In: *Buletinul Academiei de Științe a Moldovei. Științe medicale*. Chișinău, 2017, nr. 2(54), pp. 21-27. ISSN 1857-0011.
2. Bradu, A., Ceban, E. Istoria mondială și autohtonă în dezvoltarea litotritiei extracorporale cu unde de șoc. In: *Buletinul Academiei de Științe a Moldovei. Științe medicale.* Chişinău, 2017, nr. 3(55), pp. 144-148. ISSN 1857-0011.
3. Banov, P., Ceban, E. Renal calculi chemical composition in patients with recurrent nefrolithiasis in the Republic of Moldova. In: *Moldovan Journal of Health Sciences*. Chisinau, 2015, vol. 5, nr. 3, pp. 44-53. ISSN 2345-1467.
4. Ceban, E. The treatment of the reno-ureteral calculi by extracorporeal shockwave lithotripsy (ESWL). In: *J. Med. Life*, 2012 June 12; nr. 5(2), pp. 133–138.
5. Ceban, E. *Tratamentul litiazei renoureterale prin litotritie extracorporală cu unde de şoc (ESWL). Indicaţii metodice*. Chișinău: CEP Medicina, 2015, 26 p. ISBN 978-9975-118-95-8.
6. Ceban, E. *Tratamentul multimodal al nefrolitiazei complicate*. Chișinău: CEP Medicina, 2013. 216 p.
7. Ceban, E., Banov, P., Oprea, A. et al. Role of computer tomography in predicting urinary stone composition. European Urology supplements. In: *Abstracts of the 2nd Meeting of the EAU section of Urolithiasis 5-7 september 2013*. Copenhagen, 2013, vol. 12, nr. 3, p. 79.
8. Geavlete, P. Optimizing shock wave lithotripsy in the 21st century: Editorial Comment. In: *Eur. Urol*., 2007, nr. 52(2), pp. 352-353.
9. Glybochko, P.V. The clinical role of X-ray computed tomography to predict the clinical efficiency of extracorporeal shock wave lithotripsy." *Urologia Journal* 86.2 (2019): 63-68.
10. Kim, J. W., Chae, J. Y., Kim, J. W. et al. Computed tomography – based novel prediction model for the stone-free rate of ureteroscopic lithotripsy. In: *Urolithiasis*, 2014, nr. 42, pp. 75–79.
11. Tiselius, H., Alken, P., Buck, C., et al. *Guidelines on urolithiasis*. European Association of Urology, 2018. 128 p.
12. Tiselius, H. Words of wisdom. Re: Prevalenceof kidney stones in the United States. In: *Eur. Urol*., 2012, nr. 62, pp. 936–937.
13. Zhe, M., et al. Nephrolithiasis as a risk factor of chronic kidney disease: a meta-analysis of cohort studies with 4,770,691 participants. In: *Urolithiasis*, 2017, nr. 45, p. 44.

14. Shan, N. Patient profile & outcome in cases of proximal ureteric calculus treated wirh ESWL compared to other procedure. *International Journal of Scientific Research*. – 2020. – T. 9. – №. 1.
15. Qattan, M. M. Stone-free rate after extracorporeal shockwave lithotripsy in the management of renal stones in relation to different sizes and locations of the stone, 2020.T. 7. №. 10. C. 49. *Middle East Journal of Family Medicine*.
16. Matas, A., Beltran, B., Rios, J. et. al. PD26-01 Ultrasound guided extracorporeal shok wave litotripsy. *Journal of Urology*, (2019),(Supplement 4), e473-e474.
17. Charles, D. Scales, Jr., Alexandria, C. et. al. Prevalence of Kidney Stones in the United States. *Eur Urol*. 2019 July; 62(1): 160–165
18. Cook, J., Lamb, B. W., Lettin, J. E. et.al. The epidemiology of urolithiasis in an ethnically diverse population living in the same area. *Urology journal*, (2016), *13*(4), 2754-2758.
19. Turk, C. EAU *Guidelines on Interventional Treatment for Urolithiasis. Eur Uro*l, 2018. 69: 475.
20. Roger, F. Diagnostic Accuracy of Low and Ultra-Low Dose CT for Identification of Urinary Tract Stones: *A Systematic Review. Urol Int*, 2019. 100: 375.
21. Skolarikos, A. The Efficacy of Medical Expulsive Therapy (MET) in Improving Stone-free Rateand Stone Expulsion Time, After Extracorporeal Shock Wave Lithotripsy (SWL) for Upper Urinary Stones: *A Systematic Review and Meta-analysis. Urology*, 2015. 86: 1057.
22. Perekalina, A. The clinical role of X-ray computed tomography to predict the clinical efficiency of extracorporeal shock wave lithotripsy. *European Urology Supplements* 17.2 (2018): e1813.

INFORMATION ON VALUATION OF RESEARCH RESULTS

- **Articles in international scientific journals (abroad):**

  - **articles in journals Scopus, Pubmed, Pubmed Central, Index Copernicus and other international databases**

1. **Bradu A**., Banov P., Ceban E. Efectiveness of combined therapy in the treatment of urolithiasis. *Archives of the Balcan Medical Union*. 2020, vol 55, nr. 2, p. 11-17. ISSN 1584-9244.
2. **Bradu A. Bradu A.**, Ceban E. Necessity of antibacterial prophylaxis in the treatment of reno – ureteral lithiasis by shock wave lithotripsy – a prospective descriptive study. *Archives of the Balcan Medical Union*. 2020, vol. 55, nr. 2, p. 40-45. ISSN 1584-9244. (IF: 1.12)

- **Articles in accredited national scientific journals:**

  - **articles in category B journals**

3. **Bradu A**. Rolul litotriției extracorporeale cu unde de șoc în tratamentul litiazei reno-ureterale. *Buletinul Academiei de Științe a Moldovei. Științe Medicale.* Chișinău, 2017, nr. 2(54), p. 21-27. ISSN 1857-0011.
4. **Bradu A**., Ceban E. Istoria mondială și autohtonă în dezvoltarea litotriției extracorporeale cu unde de șoc. *Buletinul Academiei de Științe a Moldovei. Științe Medicale*. Chişinău, 2017, 3(55), p.144-148. ISSN 1857-0011.
5. Ceban E., Banov P., Galescu A., **Bradu A**. et. al. Studiul imunității celulare și umorale la pacienți cu urolitiază complicată. *Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţe Medicale*. Chişinău, 2017, 2(54), p.194-200. ISSN 1857-0011.
6. **Bradu A.,** Galescu A., Oprea A., Ceban E. ESWL la etapa actuală: indicaţii, rezultate, eficacitate, complicaţii. *Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţe Medicale*.

Chişinău, 2014, 4(45), p.145-148. ISSN 1857-0011.

- **articles in category C journals**

7. **Bradu A**. Concepte și principii fizice ce stau la baza dezintegrării calculilor prin litotriție extracorporeală cu unde de șoc. *Arta Medica*. 2019, nr. 1(70), p. 39-41. ISSN 1810-1852.
8. Banov P., Ceban E., **Bradu A.** et. al. Eficacitatea utilizării extractului din Agropyron Repens în tratamentul urolitiazei. *Arta Medica.* 2019, nr. 1(70), p. 36-38. ISSN 1810-1852.
9. Galescu A., Dumbrăveanu I., Ivanov M., Banov P., **Bradu A.** et. al. Schimbările anatomiei ecografice renale postoperatorii la pacienţii cu litiază coraliformă. *Arta Medica.* 2019, nr. 1(70), p.29-35. ISSN 1810-1852.
10. **Bradu A.,** Ceban E., Galescu A., Oprea A. Strategii terapeutice în „steinstrasse" după litotriția extracorporeală cu unde de șoc. *Arta Medica.* 2019, nr. 1(70), p. 45-47.ISSN 1810-1852.
11. **Bradu A.,** Ceban E., Galescu A., Banov P. et. al. Urocultura – conduita administrării de antibiotice pre- și post litotriție extracorporeală cu unde de șoc. *Arta Medica.* 2019, nr. 1(70), p. 42-44. ISSN 1810-1852.
12. **Bradu A.,** Ceban E. Rolul densitometriei prin tomografie computerizată în evaluarea rezultatelor tratamentului prin litotriție extracorporeală cu unde de șoc al calculilor renoureterali: studiu prospectiv, descriptiv. *Moldovan Journal of Health Sciences.* Chișinău, 2017, vol. 12, nr. 2, p. 32-38. ISSN 2345-1467.
13. **Bradu A.,** Ceban E., Galescu A. et. al. Analiza complicaţiilor post ESWL în tratamentul litiazei renoureterale. *Arta Medica.* 2015, nr. 4 (57), p. 22-25. ISSN 1810-1879.
14. Galescu A., Ceban E., Banov P., Botnari V., **Bradu A.** et. al. Indicii imunităţii umorale în litiază renală coraliformă. *Arta Medica*. 2015, nr. 4 (57), p. 15-18. ISSN 1810-1879.

- **Articles in scientific conference proceedings:**

- **national conferences with international participation**

15. **Bradu A**., Ceban E., Galescu A. et. al. Analiza complicaţiilor post ESWL în tratamentul litiazei renoureterale. *Al VI-lea Congres de Urologie*, *Dializă şi Transplant Renal din Republica Moldova cu participare internaţionlă. Arta Medica*. 2015, nr. 4 (57), p. 22-25. ISSN 1810-1852.
16. **Bradu A.,** Lupașcu C., Tănase A. et. al. Pielonefrita acută în practica urologică – etiologie, diagnostic, tratament. *Al VI-lea Congres de Urologie, Dializă şi Transplant Renal din Republica Moldova cu participare internaţionlă Arta Medica.* 2015, nr. 4 (57), p.70-72. ISSN 1810-1852.
17. Galescu A., Ceban E., Banov P., Botnari V., **Bradu A.** et. al. Indicii imunităţii umorale în litiază renală coraliformă. *Al VI-lea Congres de Urologie, Dializă şi Transplant Renal din Republica Moldova cu participare internaţionlă Arta Medica.* 2015, nr. 4 (57), p. 15-18. ISSN 1810-1852.

- **Theses in scientific conference proceedings:**

- **international conferences held in the Republic of Moldova**

18. **Bradu A.** The role of tamsulosin administration in evolution of stone clearence after ESWL for ureteral stones. *Abstract book. The 7th International Medical Congress for Students and Young Doctors.* Chişinău, 2018, p.123. ISBN 978-9975-47-174-9.
19. **Bradu A.** Complications and their prevention after extracorporeal shock wave lithotripsy (ESWL*). Abstract book. Sixth International Medical Congress for Students and Young Doctors*. Chişinău, 2016, p.179. ISBN 978-9975-3028-3-8.

- **international conferences held abroad (ProQuest, EBSCO databases)**

20. **Bradu A**., Ceban E., Galescu A. et. al. Litotriția extracorporeală cu unde de șoc în tratamentul calculilor ureterali. Materialele Congresului Asociației Române de Urologie. *Al XXXIII-lea Congres al Asociaţiei Române de Urologie. Revista Română de Urologie.* 2017, vol 16, nr. 2, p. 66. ISSN 1223-0650.
21. Ceban E., Banov P., Galescu A., **Bradu A**. et. al. Modificările imunologice în urolitiaza complicată. Materialele Congresului Asociației Române de Urologie. *Al XXXIII-lea Congres al Asociaţiei Române de Urologie. Revista Română de Urologie.* 2017, vol 16, nr. 2, p. 66. ISSN 1223-0650.
22. Ceban E., Banov P., Galescu A., **Bradu A.** et. al. The peculiarities of chemical composition of kidney stones in patients with recurrent urolithiasis in Republic of Moldova. *Al XXXII-lea Congres al Asociaţiei Române de Urologie. Revista Română de Urologie*. 2016, vol 15, nr. 2, p. 73. ISSN 1223-0650.
23. **Bradu A**., Ceban E., Galescu A. et. al. Litotriţia Extracorporeală cu Unde de şoc în tratamentul calculilor renu-ureterali. Experienţa de peste 1800 pacienţi. *Al XXXII-lea Congres al Asociaţiei Române de Urologie. Revista Română de Urologie*. 2016, vol 15, nr. 2, p. 60. ISSN 1223-0650.

- **Reports at scientific forums:**

- **international forums**

24. **Bradu A**., Ceban E., Galescu A. et. al. Litotriția extracorporeală cu unde de șoc în tratamentul calculilor ureterali. Materialele Congresului Asociației Române de Urologie. *Al XXXIII-lea Congres al Asociaţiei Române de Urologie. Revista Română de Urologie*.. 2017, vol 16, nr. 2, p. 66. ISSN 1223-0650.
25. **Bradu A**., Ceban E., Galescu A. et. al. Litotriţia Extracorporeală cu Unde de şoc în tratamentul calculilor renu-ureterali. Experienţa de peste 1800 pacienţi. *Al XXXII-lea Congres al Asociaţiei Române de Urologie. Revista Română de Urologie*. 2016, vol 15, nr. 2, p. 60. ISSN 1223-0650.

- **national forums** with **international participation**

26. **Bradu A.** The role of tamsulosin administration in evolution of stone clearence after ESWL for ureteral stones. *The 7th International Medical Congress for Students and Young Doctors.* Chişinău, 2018, p.123. ISBN 978-9975-47-174-9.
27. **Bradu A.** Complications and their prevention after extracorporeal shock wave lithotripsy (ESWL*). Sixth International Medical Congress for Students and Young Doctors.* Chişinău, 2016, p.179. ISBN 978-9975-3028-3-8.