UNIVERSITY OF MEDICINE AND PHARMACY CRAIOVA
DOCTORAL SCHOOL

PhD THESIS
-ABSTRACT-

EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY (ESWL) EFFECTIVENESS AND COMPLICATIONS IN UROLIHIASIS TREATMENT

PhD SUPERVISOR
Prof.univ.dr. ANDREI BONDARI

PhD STUDENT
Dr. MIHAI CRISTIAN NEDELCUȚĂ

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ABBREVIATION

CIRF - Clinical Insignifiant Residual Fragments

CT – Computer Tomography

EAU – European Association of Urology

ESWL – Extracorporeal Shock Wave Lithotripsy

HTA – Arterial Hypertension

HU – Hounsfield units

PCNL – Percutaneous Nephrolithotomy

KUB X-RAY – Kidney, Ureter And Bladder X-Ray

ROI - Region Of Interest

Sf - Specificity

Sn - Sensitivity

IVU – Intravenous Urography

URS - ureterorenoscopy

FNV - Falsely Negative Value

INTRODUCTION

Urinary lithiasis is an important health problem worldwide with an estimated prevalence in the general population of 2-3% and a lifetime recurrence rate of about 50%. The apparent increase in the incidence may be the result of real growth, but also due to asymptomatic stones detection imaging investigations more efficient.

There has been made significant progress in the minimally invasive treatment methods, but also to deepening lithogenesis and in terms of diagnosis, CT became the standard method in the investigation of renal colic, a method that we hope will also become standard in our protocol diagnosis.

With the introduction of extracorporeal lithotripsy into therapeutic algorithm of the lithiasic patient, this method has become the treatment of choice for kidney stones less than 2 cm, and due to the progress made between 80 and 90% of patients with renal and ureteral stones.

The results of ESWL depend on many factors such as the size calculi, location, chemical composition, fragility, device type, the presence of obstruction or infection, but with the introduction of the concept of fragility of stone, chemical composition became the main factor that influenced the effectiveness of ESWL.

In the thesis entitled *"Extracorporeal shock wave lithotripsy (ESWL) for urolithiasis treatment Effectiveness and Complications"* I proposed to assess rates of "stone-free" in patients with kidney stones treated with ESWL using different parameters of device to improve the accuracy of treatment. I also proposed to determine the influence of parameters on the occurrence and severity of complications fragmentation of this treatment method.

I would like to thank Prof. Dr. Andrei Bondari for the support given to me in developing this scientific thesis, whose extensive training and professional experience is an example for all initiated in medical practice.

I. State of knowledge

Urolithiasis is a disease known since ancient times, the prevalence of the disease is between 2% and 3% [1]. The probability of a man to develop a stone by the age of 70 years is 1-8 [2]. The incidence of urinary stones was about three times higher in men and women, recently reaching 1.7:1 ratio [3] and in the United States in 1994, it was estimated lithiasis disease prevalence from 6.3% in among men and 4.1% among women [4], but a recent analysis shows an increase of healthcare resources used to treat patients with urinary stones [2,3], 1 in 11 individuals suffering from this condition in the U.S. [5].

The apparent increase of incidence may be the result of real growth, but also due to asymptomatic stones detection imaging investigations more efficient, requiring treatment methods and the emergence of minimally invasive and provide a quick resolution of the condition. Since in the early 1980s [6], the method with extracorporeal shock wave lithotripsy (ESWL) has revolutionized the treatment of urinary stones, especially the upper urinary tract.

The method is based on the disintegration of calculi by shock waves produced outside the body, who penetrates tissues without causing damage to them, acting through several mechanical and dynamic forces, the most important being considered cavitation [7]. Continuous improvement of extracorporeal lithotripsy equipment and endoscopic instruments has completely overturned the treatment indications of reno-ureteral stones and that replaced the open surgery [8]. Added to this pressure wave of patients that require new methods of treatment due to reduced clinical distress (disappears surgical wound) and rapid social and family reintegration (outpatient treatment or inpatient minimum) [9].

Over time, there have been significant advances in the minimally invasive treatment methods, but also to deepen lithogenesis [10], until the 1980s, many patients needing extensive surgery, approximately 20% of patients with recurrent lithiasis which required multiple surgeries have developed a degree of renal impairment [11]. Due to the progress made, between 80 and 90 % of patients with urolihiasis are treated by ESWL, 8-10 % by endourological procedures (PCNL, ureterorenoscopy) and only 1-2% by open surgery [12].

II. The importance of the problem addressed

With the development of investigative and diagnostic methods, CT scan has become the standard method in the investigation of renal colic, which we hope will become a standard method in our diagnostic protocol. Compared with KUB x-ray, abdominal ultrasound and IVU, CT scan has higher ability to detect urinary calculi by you differentiate from other

ureteral obstruction (clot, stricture, neoplasia) and identify back pain of non-urological causes [13, 14].

SWL results do depend on stone size, location, composition, fragiliy, device type and the presence of obstruction or infection [15]. The lithotripter evolution led to the appearance of III and IV generation equipment, more secure, easier to use, the possibility to perform the procedure without anesthesia, electromagnetic wave energy stability, tuning range extended wave intensity and the possibility of permanent adjustment them during the procedure [8]. All this allowed the procedure to be carried out even by well trained technicians [16].

This procedure is performed in over 95% of cases without anesthesia on an outpatient or one day hospitalization [12].

Although the extracorporeal lithotripsy treatment is a method which has many complications, the destructive forces generated by the cavitation phenomenon can lead to various complications, which may cause trauma to the blood vessels of the kidney and adjacent tissue, resulting in bleeding and release of cytokine and inflammation response [17].

So I tried to reduce the occurrence of complications, at least thr minor ones by changing various parameters used in extracorporeal lithotripsy, such as frequency, intensity and number of shock waves. At the same time we assessed the procedure effeciency and hoping that reducing complications number, we will not change the effectiveness of SWL, which is very high.

III. Objectives

This study, entitled "*Extracorporeal shock wave lithotripsy (ESWL) effectiveness and complications in urolithiasis treatment*" proposed as first objective to assess the role of extracorporeal lithotripsy in urolithiasis, including "stone-free" rates and efficiency analysis of SWL, managing and improving the efficiency of urolithiasis diagnosis and treatment. We also proposed to establish SWLcomplications rates, their rates depending on the fragmentation characteristics and the measures needed to overcome them.

IV. Methods

This prospective study was conducted during October 2008 - March 2012, evaluated 1169 patients diagnosed with kidney stones who were treated by extracorporeal lithotripsy (SWL) in „PRIMA MEDICAL” Clinic Craiova, but just 644 patients who had single stones entered the study.

Following the extracorporeal lithotripsy using afrequency of 1 or 2 shock waves/second, the patients were divided into two groups: 315 patients were treated by 1 shock wave/second, and 329 patients were treated with 2 shock waves/second.

The study included patients who had unique kidney stones, with a diameter less than 25 mm and with functional kidney. All patients performed biochemistry, hematology and urinalysis. Each patient who entered the study, has been diagnosed with kidney stones by IVU or CT scan. All were treated by SWL, on an outpatient basis without anesthesia, using a third generation electromagnetic Lithotripter - STORZ © Modulith SLK. The repeted procedures were permormed between 14 and 30 days.

Indication of active removal of a renal calculus was based on the recommendations of the European Association of Urology [18].

Primary and statistical analysis of data was performed using MS Excel software and MedCalc 10.2 (*MedCalc Software bvba, Belgia*).

All the activities mentioned were performed in urology and radiology clinics in Craiova Emergency County Hospital, UMF Craiova and the "PRIMA MEDICAL" Clinic, where we performed lithotripsy.

We conducted this investigation and treatment methods taking into account ethical and moral principles of the Helsinki Declaration of Human Rights, the most important factors taken into account were the well-being and safety of subjects. All subjects consented for voluntary participation.

V. Results

a. Epidemiological data

Ages of the 644 patients were between 15 and 84 years, with a mean of 50.5 ± 15.4 years. Incidence of urinary stones was about 3 times higher in men compared to women, recently it reached 1.7:1 ratio, as evidenced in our study the sex ratio was 1.63:1 male:female.

Of the 644 enrolled patients, 303 patients (47%) had personal or family history of disease or other conditions lithiasic that were considered relevant to the developmental urolithiasis:

- family history of the disease lithiasic - 107 cases (16.6%),
- personal history of disease lithiasic - 81 cases (12.6%),
- chronic urinary tract infections or recurrent - 49 cases (7.6%),
- obesity - 38 cases (5.9%),

• diabetes - 28 cases (4.3%).

There were no epidemiological statistically significant differences between the two study groups regarding mean age, distribution by age, sex, origin, daily fluid intake or urological history.

b. Clinical data

Most patients (310 - 48.1%) had back pain, for which there was no need to start a painkiller or anti-inflammatory treatment. There were 167 patients (25.9%) whit haematuria, 101 patients (15.7%) had diffuse abdominal pain, 92 patients (14.3%) had microscopic hematuria and for 83 patients (12.9%) the stone was dicovered at a routine ultrasound check for other conditions. Renal ultrasound has proven remarkably effective in highlighting a kidney stone, the examination was suggestive in 532 of the 644 cases studied - Sn = 82.6%..

There were 352 patients (54.7%) investigated by IVU, but only 283 patients were diagnosed and underwent extracorporeal lithotripsy without needing other investigations and the sensitivity was 80.4%.

All 361 patients who had a CT scan, had high efficiency, identifing the calculi in all the 361 cases (Sn = 100%).

c. Tomographic and IVU data

Maximum stone size was calculated on the image which was the largest either longitudinal or transverse. Stone sizes were between 7 and 25 mm, with a mean of 12.5 ± 3.8 mm.

We found that 70% of stones less than 10 mm were not identified on IVU, this had specificity of 79.7% and sensitivity of 69.6%, and chance to discover a stone on IVU is less than 10 mm, being less than 30%, such as in Figure 1.

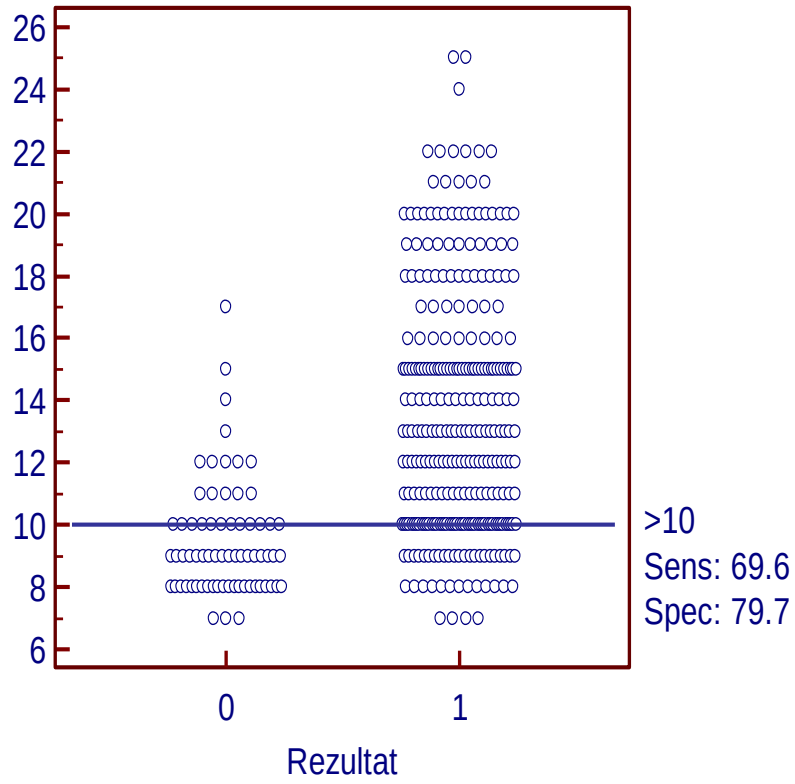

Figure 1. "Dot diagram" analysis for the threshold below which the stone discovery rate by IVU decreases ($p<0.001$)

All these results show that CT was able to identify several small calculi unlike intravenous urography, which strengthens tomography using the standard method of diagnosis of urinary stones.

d. Data on calculi chemical composition

We performed chemical analysis of the stones for only 259 patients (40.2%). We considered the main component of the calculi, so patients had calcium oxalate calculi, 1131 patients (50.6%), of which 16.2% were calcium oxalate monohydrate and 34.4% dihydrate, 83 patients (32%) had uric acid stones, 31 patients had phosphate-ammonium-magnesium calculi (12%), while 14 patients had cystine calculi (5.4%).

e. Data on extracorporeal lithotripsy

Of the 644 patients, 511 (79.3%) were "stone-free" within 90 days after the first SWL session, while 133 patients (20.7%) of them showed more than 5 mm residual fragments or required ureteroscopy for steinstrasse in this period.

In terms of the sessions number that were conducted in our study, 262 patients (40.7%) needed one session to complete fragmentation, 162 patients (25.2% s) needed 2

sessions, 120 patients (18.6%) needed 3 sessions, 70 patients (10.9%) required four sessions, while 30 patients (4.6%) needed 5 sessions.

In group 1, the average of shock waves received by each patient was 4731±2634, while the average lithotripsy shock waves per session was 2302±306, with an average intensity of 61.1±3.8 kV, the average rate used was 1 shock waves/second, the average number of sessions was 2.1±1.1.

For patients in group 2, the average of shock waves received by each patient was 8509±4894, while the average shock waves per session was 3883±324, with an average intensity of 55.1±4.7 kV, the average rate used is 2 shock waves/second, the average number of sessions was 2.2±1.3.

f. Analysis of treatment effectiveness and prognosis

The "stone-free" rate in group 1 was 81.3% and in 77.5% group 2, which means that the use of low shock waves frequency does not change SWL efficiency.

In patients with large stones SWL efficiency is higher at a frequency of 1 shock wave/second ($p<0.05$, Fisher exact test). With the increase of stone size, increases the number of SWL sessions, which means that patients with high stone dimensio must be selected carefully for lithotripsy.

We performed Kaplan-Maier analysis to observe the "stone-free" rate according to the chemical composition and found statistically significant differences ($p<0.001$) in both groups, which has demnostrate that patients who had acid calculi uric had a rate much higher than the patients who had calcium oxalate monohydrate calculi, but also to those of cystine and the calcium oxalate dihydrate, as can be seen in Figures 2 and 3.

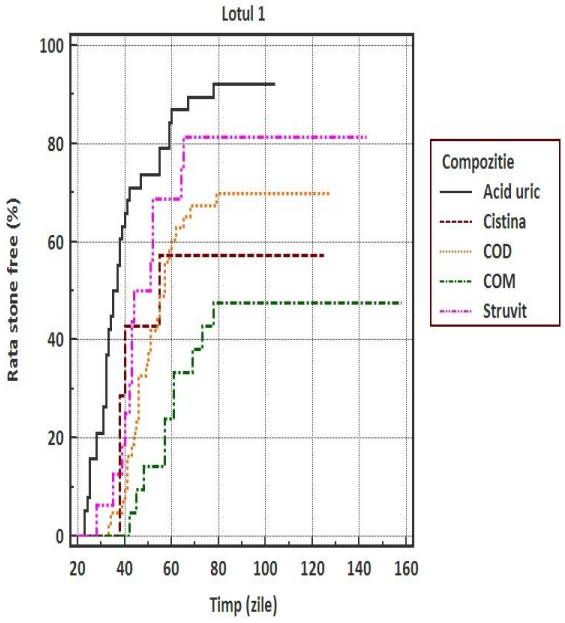

Figure 2. The evolution toward the "stone free" for patients in Group 1 according to the chemical composition of calculi (p<0.001)

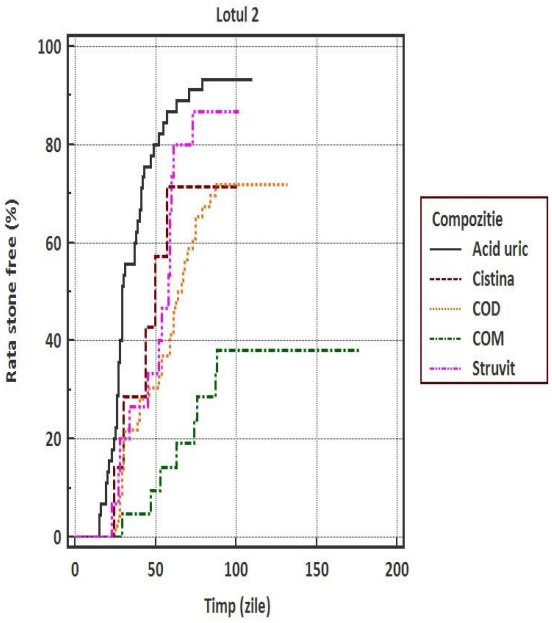

Figure 3. The evolution toward the "stone free" for patients in Group 2 according to the chemical composition of calculi (p<0.001)

I checked the number of shock waves required for fragmentation and I found a threshold value of 5983 shock waves with Sn=80.1% and Sf=91.5%, indicating that if lithotripsy is performed with 1 shock waves/second and fails after 6000 pulses, the chance of fragmentation is below 10% (p<0.001) - Figure 4. The same threshold for patients with 2 shock waves/second is 12.032, which has Sn=96.5% and Sf=77%, and the stone is not fragmented after 12.000 shock waves, that chance is below 5% (p<0.001) - Figure 5.

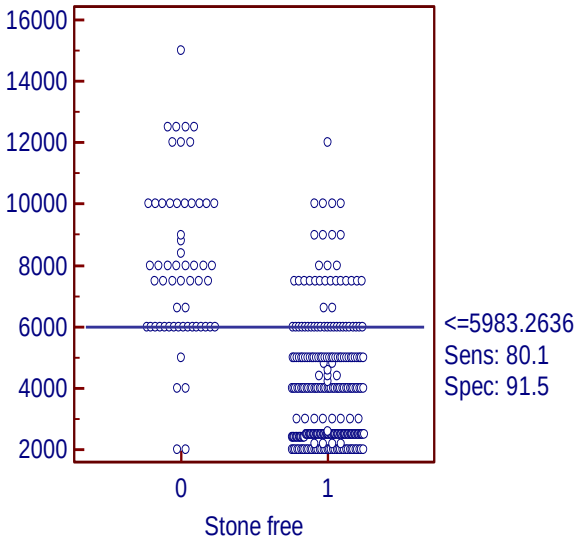

Figure 4. "Dot diagram" analysis the threshold where SWL is becoming less effective for patients of Group 1 (p<0.001)

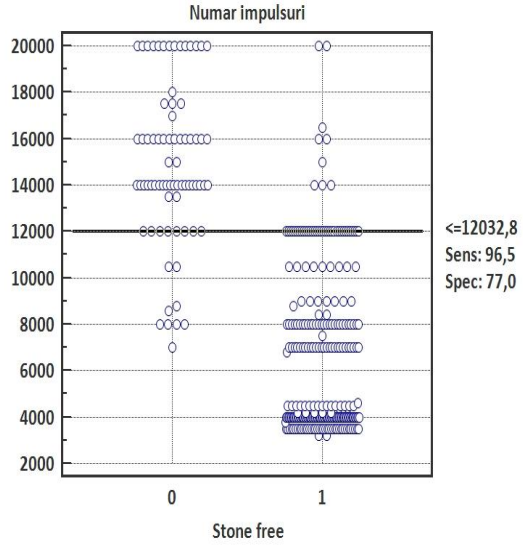

Figure 5. "Dot diagram" analysis the threshold where SWL is becoming less effective for patients of Group 2 (p<0.001)

g. SWL complications

There were no serious complications which required radical surgery, there were 7 cases (1.1%) of subcapsular hematoma, which required only rest and surveillance, and 72 cases (11.2%) of steinstrasse, which required retrograde ureteroscopy.

As regards the distribution of patients with complications in the two groups, in group 1 there were 106 patients (20.9%) who experienced at least one complication, while in Group 2 were 175 patients (53.2%), the difference being highly statistically significant ($p<0.001$, Chi-square test, RR = 0.7055 (95% CI = 0.6136-0.8111), as can be seen in Figure 6.

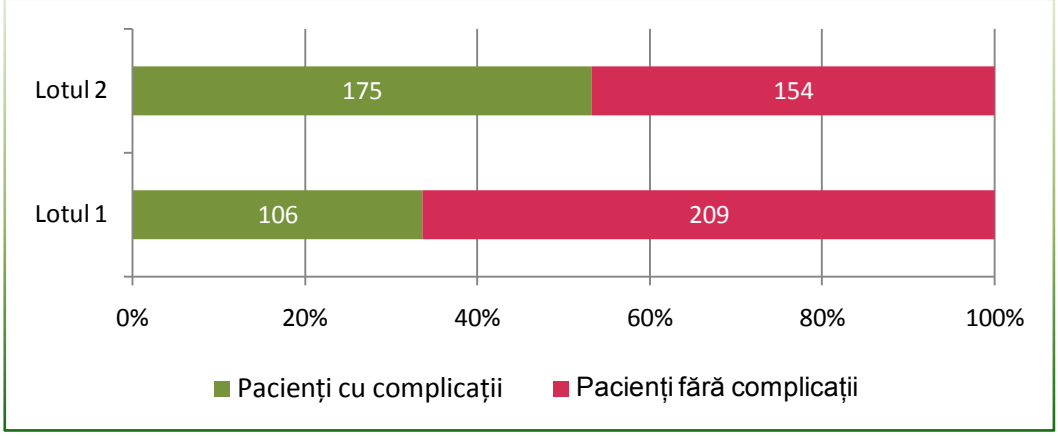

Figure 6. The overall incidence of complications was significantly lower in group 1 ($p<0.001$).

Distribution of minor complications in the two groups can be seen in Figure 7, more complications occured in group 2.

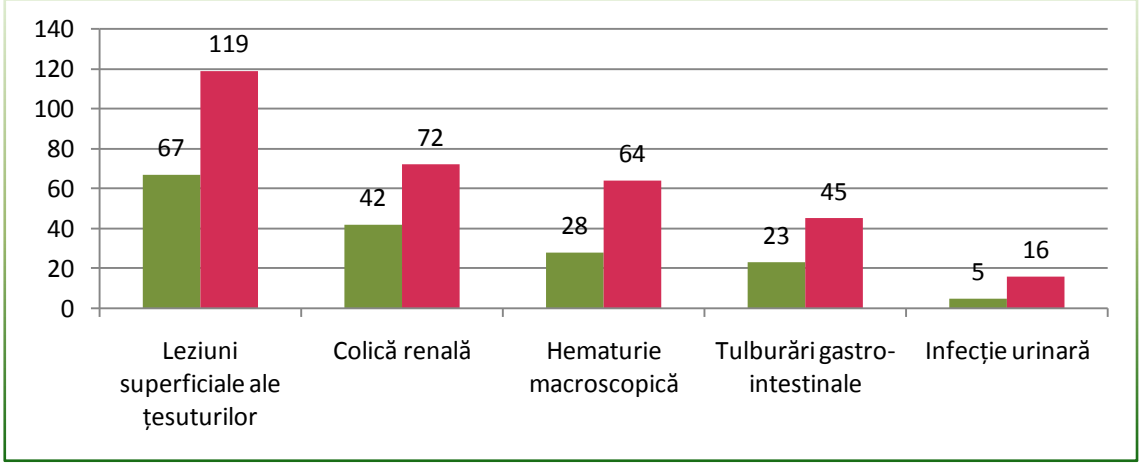

Figure 7. Distribution of minor complications showed statistically significant differences between the two groups

The threshold of SWL complications in Group 1 are becoming increasingly common after more than 2100 shock waves/session, with Sn = 64.2% and Sp = 84.3% - Figure 8. The same threshold for patients in Group 2 is 3900 shock waves/session, which is Sn = 92.6% and Sp = 64.9% - Figure 9.

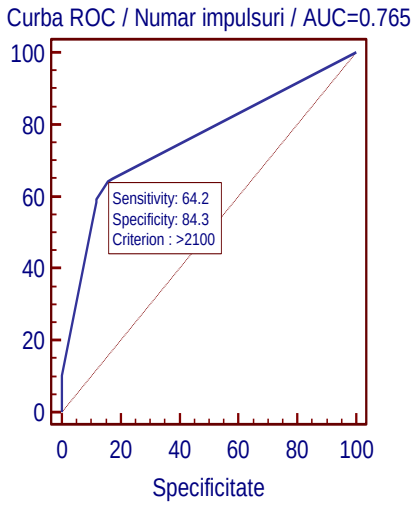

Figure 8. ROC curve for discovering the maximum number of shock waves required to avoid complications in group 1, the area under the curve AUC = 0.765 (p<0.001)

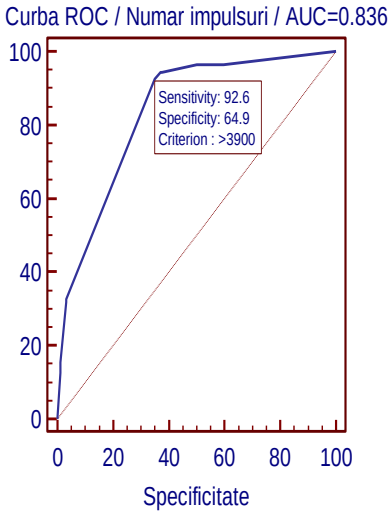

Figure 9. ROC curve for discovering the maximum number of shock waves s required to avoid complications in group 2, the area under the curve AUC = 0.836 (p<0.001)

Even if there were no significant differences in lithotripsy efficiency of, reduced complications appeared while reducing the number and frequency of the shock waves, lead to the conclusion that the optimal frequency to be used is 1 shock waves/second.

VI. Discussion

The results of SWL are quantified in terms of fragmentation and the complete elimination of the compilation and that depends on the size and chemical composition of the calculation [10, 15], so that the ability to predict the chemical composition would increase the effectiveness of SWL.

The results of SWL are weaker in the case of the approach of the lower caliceal, stone-free rate of 41-70% [19].

There are still numerous controversies about the effectiveness of the various lithotriptor models [20]. The new model used, electromagnetic generation III -STORZ Modulith SLK © proves to be very efficient, being accompanied by a high comfort for patient and doctor.

Complications related to fragmentation of calculi can be prevented by limiting the use of SWL for large kidney stones and using PCNL, steinstrasse appearing at 1%-4% of patients in the SWL [21]. The rate increases to 5%-10% of patients with large stones (> 2 cm) [22], and up to 40% in patients with partial or complete staghorn [23].

The ureter cateterization before SWL reduces the complications caused by residual fragments, especially when it's fragmented a large stone [24]. Recently, Okeke has successfully used a ureteral access sheath combined with SWL fragments to facilitate passage lithiasis in patients with large calculi when PCNL was contraindicated [25].

In connection with the side effects, our results were similar to most authors, and in a study of 736 cases treated by SWL, only 24 patients (3.3%) were associated with major side effects in this study, as we do not considered transient hematuria of low-intensity and moderate pain in the flank as the major complications [26].

Into a meta-analysis of randomized controlled studies have shown that the use of prophylactic antibiotics routinely to all patients treated by SWL is effective and efficient in reducing the need for treatment in patients with urosepsis [27]. However, several studies, including randomized controlled trials [28], have not shown a advantage of antibiotics administered prophylactically in patients without preoperative UTI or calculi [28].

The introduction of new lithotriptors, which are easy to use, treatment is only moderately painful, but selecting and optimizing patient treatment protocols are needed to maximize the percentage of "stone-free" and to minimize side effects.

VII. Conclusions

- IVU sensitivity was only 80%, while the sensitivity of CT scan was 100%.
- IVU sensitivity to discover the calculi of less than 10 mm was only 18.9%.
- CT scan was able to identify several small calculi unlike intravenous urography, which strengthens CT scan as the standard method of diagnosis of urinary stones.
- The use of a low frequency shock waves does not change the effectiveness of extracoporeal lithotripsy. But in patients with large stones SWL efficiency is higher at a frequency of 1 shock wave/second.
- If lithotripsy is performed with 1 shock waves/second and fails after 6000 pulses, the chance of fragmentation is below 10% ($p<0.001$). If its performed with 2 shock waves/second and the stone is not fragmented after 12.000 shock waves, that chance is below 5% ($p<0.001$)
- In group 1 were 106 patients (33.6%) who had at least one complication, while in group 2 were 175 patients (53.2%) ($p <0.001$).
- Performing SWL with 1 shock wave/second, significantly reduce the complications and the maximum number of shock waves used in one session should be 2100. If the procedure is carried out with 2 shock wave/session, the maximum number of shock wave should be 3900.
- Even if there were no significant differences in lithotripsy efficiency of, reduced complications appeared while reducing the number and frequency of the shock waves, lead to the conclusion that the optimal frequency to be used is 1 shock waves/second.
- Preventive measures may be taken to reduce the frequency of these side effects. Modern Lithotriptors are increasingly easier to use, is only a moderately painful treatment, but patients selection and optimization of treatment protocols are needed to maximize "stone - free" rates and minimize the side effects.
- Besides medical treatment, ESWL is the only non-invasive therapy for kidney stones, with superior results, it’s a safe procedure with a low rate of complications that can be applied repeatedly.

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