PHD THESIS
-ABSTRACT-

THE PREDICTIVE VALUE OF CT SCANNING ON THERAPEUTIC EFFECTIVENESS OF EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY

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ABBREVIATION

**CIRF** - Clinical Insignificant 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
**Sn** - Sensitivity
**Sn** - Specificity
**IVU** – Intravenous Urography
**FNV** - Falsely Negative Value
INTRODUCTION

Urinary lithiasis is an important health problem worldwide with an estimated prevalence in general population of 2-3% and a lifetime recurrence rate of about 50%. The apparent increase in the incidence may be real because of early detection of asymptomatic lithiasis using advanced imaging investigations. There has been significant progress regarding minimally invasive treatment methods, also there is a better understanding of 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 shock wave lithotripsy into therapeutic algorithm of the lithiastic patient, the method has become the treatment of choice for kidney stones with a diameter less than 2 cm, therefore almost 80 - 90% of patients with renal and ureteral stones are treated by ESWL.

ESWL results depend on many factors such as size stone location, 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 "The predictive value of CT scanning on therapeutic effectiveness of extracorporeal shock wave lithotripsy", I wanted to evaluate the role of computed tomography in determining the rates of fragility of calculi and "stone-free" in patients with kidney stones treated with ESWL, which facilitates imagistic urolithiasis diagnosis and can affect treatment accuracy. We aimed to establish the possibility of determining the chemical composition of calculi, based on their CT characteristics.

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 known since antiquity, and its prevalence is between 2% and 3% [1], the probability for a man to develop a calculi by the age of 70 is 1 in 8 [2]. The incidence of urinary calculi was about three times higher in men than women, recently reaching 1.7:1 ratio [3].

In 1994, data from the National Health and Nutrition Examination Survey (NHANES) estimated the prevalence of stone disease at 6.3% among men and 4.1% among women [4]. More recent analysis shows an increase of healthcare resources used to treat patients with urolithiasis [2, 3], and 1 in 11 individuals are suffering from this condition in the U.S. [5].

The apparent increase in the incidence may be the result of real growth, but also due to more efficient detection of asymptomatic stones by imaging investigations.

There has been significant progress in the minimally invasive treatment methods and deepening lithogenesis [6]. Until the 1980s urinary stones represented a major health problem, about 20% of patients with recurrent urolithiasis which required multiple surgeries have developed a degree of renal impairment [7].

In recent years, computerized tomography (CT) has become the standard method in the investigation of renal colic, which we hope will become the standard method in our diagnostic protocol. Compared with KUB x-ray, abdominal ultrasound and intravenous urography, CT scan has higher ability to detect urinary calculi and differentiate between other ureteral obstructions and identify flank pain of non-urological causes [8, 9].

With the introduction of extracorporeal lithotripsy (ESWL) by Chaussy in 1980 [10], this method has become the treatment of choice for kidney stones with a diameter less than 2 cm. This method is based on the disintegration of calculi by shock waves produced outside the body (extracorporeal), which penetrates the tissues without causing damage [11].

Due to the progress made, between 80 and 90% of patients with urolithiasis 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

Since the introduction of lithotripsy in everyday practice, have sought positive and negative factors which will influence the method for the efficiency improvement. SWL results depend on many factors such as the stone size, location, composition and fragility, the type lithotripter, the presence of obstruction or infection [13]. When the concept of stone fragility
was introduced, the chemical composition has become the main factor that influenced SWL effectiveness [14].

Many tried to predict the in vivo chemical composition of urinary calculi by different techniques as pH, identification of urinary crystals, bone densitometry and radiographic studies [15, 16].

CT scan is used to distinguish between different radiolucent filling defects, using density measurement in Hounsfield units, which can differentiate stones from clots or tumors [17]. The ability to detect differences in density of up to 0.5% is attempted to be used to determine the composition and the fragility of urinary calculi [14].

Stone density varies by chemical composition, affecting its fragility, causing SWL outcome [18], so it is vital to know stone fragility before SWL, in order to increase SWL effectiveness and to reduce the number of procedures and so on the costs.

Urolithiasis incidence is growing, increasingly more individuals requiring investigation and surgical treatment for this disease. These are reasons for trying to find a more complete method of diagnosis and to provide a good prediction about the future therapeutic measures, in order to streamline and reduce treatment costs. CT scan is currently considered standard investigation for the diagnosis of urolithiasis, providing accurate information about the size, location and, most importantly, the stone density calculation (hardness), measured in Hounsfield units (HU). Recent studies suggest that the use of stone density could improve treatment outcomes in these patients, as an important prognostic factor and so may refer the patient to the therapeutic method with the greatest chance of success. Using this information we can, indeed, improve the results of SWL, the method most commonly used to treat this kind of patients.

### III. Objectives

This study, entitled "The predictive value of CT scanning on therapeutic effectiveness of extracorporeal shock wave lithotripsy", and proposed as first objective, the assessment of CT scan importance in determining the stone fragility and "stone-free" rates in patients with renal calculi treated by SWL, improving urolithiasis diagnosis and treatment efficiency and accuracy. We also proposed to determine stone chemical composition based on their CT scan characteristics.
IV. Methods

This prospective study that was conducted between January 2011 - December 2012, evaluated 209 patients diagnosed with kidney stones who were treated by extracorporeal lithotripsy (SWL) in the “PRIMA MEDICAL” Clinic Craiova.

Following the CT scan, depending on the stone density, patients were divided into three groups: 61 patients had stones with density <500 HU, 106 patients had stones with a density between 500 and 1000 HU, and 42 patients had calculi with density > 1000 HU.

The study included patients who had unique kidney stones, with a maximum diameter of 20 mm, with functional kidneys. All patients had biochemistry, hematology and urinalysis. All were treated by SWL, on an outpatient basis without anesthesia, using a third generation electromagnetic Lithotripter - STORZ Modulith SLK©.

The interval between sessions was between 14 and 30 days. All calculi fragments removed from patients were analyzed, resulting in their chemical composition, which was very important, so we could find out if indeed there is a correlation between the density and stone composition calculation and lithotripsy efficiency.

Indication of active removal of a renal calculus was based on the recommendations of the European Association of Urology [19].

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 209 patients included in the study were between 19 and 84 years, with a mean of 50.1 ± 15 years. Average age values obtained for the three groups were similar: 49.2 ± 16.9
years for group A, 49.9 ± 14.3 years and 51.9 ± 13.8 in group B, the difference between them was not statistically significant (p = 0.7356 , ANOVA).

As presented in the introduction, the incidence of urinary calculi was about three times higher in men and women, lately this ratio reached 1.7:1, as evidenced in our study, where the sex ratio for the whole group studied was 1.56:1 men.

Lack of adequate daily fluid intake is an important risk factor in the occurrence of urinary stones, usually more present in females. Data regarding fluid intake in the groups of patients showed that 69.6 % of men said they had had enough daily fluid intake and only 28.6 % of women had this habit. There were statistically significant differences in terms of habit and sex of patients (p<0.001, chi -square test), thus concluding that women who do not consume an adequate daily fluid have a higher risk of urinary stones than men do.

Of the 209 patients included in the study, 107 patients (51.2%) had personal or family stone history of disease or other conditions that were considered significant for the occurrence of urolithiasis:

- family history of the disease lithiastic - 37 cases (17.7%),
- personal history of disease lithiastic - 29 cases (13.9%),
- chronic urinary tract infections or recurrent - 18 cases (8.6%),
- obesity - 14 cases (6.7%),
- diabetes – 9 cases (4.3%).

There were no epidemiological statistically significant differences between the three study groups regarding mean age, distribution by age, sex or urological history.

b. Clinical data

Most patients (97 - 46.4%) had lumbar pain, for which there was no need to start a painkiller or anti-inflammatory treatment. There were 55 patients (26.3%) with hematuria, 34 patients had diffuse abdominal pain (16.3%), microscopic hematuria (25 - 12%) and for 24 patients (11.5%) the stone was discovered at a routine ultrasound check for other conditions.

Renal ultrasound has proven remarkably effective in highlighting a kidney stone, the examination was suggestive in 176 of the 209 cases studied - Sn = 84.2%.

All 209 patients had a CT scan, with high efficiency and was able to identify the calculi in all the 209 cases (Sn = 100%). These data showed the effectiveness of computed tomography in the diagnosis of urinary calculi, proving why it is considered the most effective method for the diagnosis of urolithiasis.
c. Tomographic data
All 209 patients included in the study performed a CT scan, analyzing the size, location, number, specific density of the stone and of the general appearance of the kidney and its condition. All of these parameters have been analyzed separately and correlated with the treatment results.

Maximum stone size was calculated on the image which was the largest either longitudinal or transverse. Stone sizes were between 7 and 20 mm, with a mean of 12.1 ± 3.4 mm.

Regarding the location of stones, 109 patients (52.1%) had left kidney stones, and for 100 patients (47.9%) was on the right side. Of these patients, 95 (45.4%) had the stone in the renal pelvis, 32 (15.3%) had upper pelvis calculi, 38 patients (18.2%) had middle caliceal calculi and 44 patients (21.1%) had lower pelvis calculi.

The patients were divided according to the stone density and the 61 patients in group A had an average of 389.4±52.2 HU, for patients in group B it was 819.1±39.6 HU, while for the 42 patients in group C the average density was 1145.6±100.1 HU.

d. Data on calculi chemical composition
We considered the main component of the calculi, so patients had calcium oxalate calculi, 107 patients (51.2%), of which 16.3% were calcium oxalate monohydrate and dihydrate 34.9%, 66 patients (31.6%) had uric acid calculi, 25 patients had phosphate-ammonium-magnesium calculi (11.9%), while only 11 patients had cystine calculi (5.3%).

We analyzed the stones chemical composition and correlated it with the density obtained from CT scans, the highest density was for calcium oxalate monohydrate stones, with an average density of 1171.8±93 HU, calcium oxalate dihydrate calculi had a density of 925±59.6 HU, the uric acid had the lowest density, with an average of 404±71 HU, phosphate-ammonium-magnesium calculi had an average density of 634.7±71.8 HU and the cystine ones had an average density of 797.4±46.4 HU. All these differences between these patients were statistically significant (p<0.001, ANOVA) which showed that the calculated density measured on CT differs depending on their chemical composition, and are closely linked to it.

e. Data on extracorporeal lithotripsy
Of the 209 patients, 157 (75.1%) were "stone-free" within 90 days after the first session, while 52 (24.9%) of them showed more than 5 mm residual fragments or required ureteroscopy for steinstrasse in this period. The mean shock wave number received by each
patient session was 3105±976, with an average intensity of 5.8±0.6 kV, the frequency used was 1 or 2 shock waves/second.

In terms of sessions number, 94 patients (44.9%) needed one session to complete fragmentation, 41 (19.6%) needed 2 sessions, 52 (24.9%) needed 3 sessions, 13 (6.2 %) needed 4 sessions, while 9 patients (4.3%) needed 5 sessions.

f. Analysis of treatment effectiveness and prognosis

We obtained different results depending on stone density, with a direct linear correlation between it and the number of sessions required for fragmentation, the average density of in patients who required one SWL session was 642±254 HU, 681±251 HU in those with two sessions, 895±257 HU for those with three, 1052±226 HU for those with four sessions and 1134±136 HU in patients who required five sessions. All these data confirm our suspicion that a high density stone requires a large number of SWL sessions or cannot be fragmented by this procedure.

Of the 61 patients who had a density of <500 HU, 55 (90.2%) required one or two SWL sessions and 58 (95.1%) of them were "stone-free" in 90 days. There were 106 patients with stone density between 500 and 1000 HU, 36 of them (34%) required three or more SWL sessions (p<0.001 compared to patients with <500 HU) and only 82 (77.4%) were "stone-free" within 90 days (p<0.001 compared with patients with < 500 HU). Of the 42 patients with stone density > 1000 HU, 32 (76.2%) needed more than three SWL sessions and only 10 patients needed less than three sessions (23.8 %) and only 17 patients (40.5 %) were "stone-free" within 90 days.

SWL success depending on stones density and size, was 100% in patients with calculi less than 10 mm in group A, 90.9% for those in group B and 66.7 % for those in group C (p<0.05, Fisher exact test). For patients who had calculi size between 11 and 15 mm, the "stone-free" rate was 100 % in group A, 71.2% for those in group B and 33.3% for those who had average stone density greater than 1000 HU (p<0.001, Fisher exact test). In patients who had calculi size between 16 and 20 mm, the "stone-free" rate was 70 % for patients with stone density of less than 500 HU, 50% for patients in group B and only 11.1% for patients in group C (p<0.05, Fisher exact test).

We tried to find an optimal threshold value for uric acid stones detection, for this purpose we performed ROC curve. We obtained a value for the area under the curve AUC = 0.997 (p<0.001) - Figure 1, so it can identify such a threshold.
Analyzing the sensitivity (Sn) and specificity (Sp) for various thresholds, we observed that a density value of 548 HU is the best threshold for identifying uric acid stones, this threshold had Sn = 97.9% and Sp = 95.45% so a falsely negative value (VFN) of 4.55%. These results can be seen in Figure 2.

The "stone-free" rates according to the chemical composition were 93.9% for uric acid stones, 84% for struvite, the results for cystine and calcium oxalate dihydrate stones were similar 72.7% and 71.2%, while the calcium oxalate monohydrate "stone-free" rate was 41.2%, and all can be seen in Figure 3 (p<0.001).

Figure 1. ROC curve for patients with uric acid calculi, area under the curve AUC = 0.997 (p<0.001)

Figure 2. The sensitivity and specificity of the detection threshold for uric acid calculi using their density

Figure 3. "Stone-free" rates according to the chemical composition (p<0.001)
Using the ROC curve we tried to find the limit where extracorporeal lithotripsy is becoming increasingly ineffective, using the density of the stone. If for calculi with density less than 500 HU effectiveness of the method is 96.7% with increasing densities observed a decrease in the efficiency of the method. We obtained a value for the area under the curve AUC = 0.828 (p<0.001), so we can identify such a threshold value, as shown in Figure 4.

Analyzing the sensitivity and specificity for different thresholds, we observed that a density value of 945 HU is the best threshold to identify the SWL boundaries, this threshold had Sn=85.35% and Sp=73.08 %, so a VFN=26.62 % - Figure 5.

These data showed that any patient who has a stone density higher of 945 HU has only 37.7% chance to have a successful SWL.

Also from this analysis it was found that the threshold of 1194 HU is the limit from where extracorporeal lithotripsy efficiency reduces, with a sensitivity of 100 % but a specificity of only 25 %.

So, for patients with a stone density of less than 500 HU we can think to use this method of treatment for even larger than 20 mm stones, together with various methods of chemolysis, which have proved to be very effective in the treatment of uric acid calculi, so we can expect increased efficiency. In patients with calculi with higher density than 945 HU this method of
treatment (SWL) should be used with caution and if after a few sessions we do not see any progress, the patient should be guided to a different treatment method. Instead, for patients with a stone density more than 1194 HU, this method should be contraindicated and therefore, the patient should be guided to PCNL or laparoscopic surgery, or even to open surgery.

VI. Discussion

The outcome of ESWL is measured in terms of fragmentation and clearance of the calculus fragments. Fragmentation of a calculus largely depends on its size and composition [6, 20], and the ability to predict stone composition would help to increase the efficiency of ESWL. NCCT is noninvasive and provides better density discrimination than conventional radiography; it can be used to detect a density difference of 0.5%, whereas plain radiography requires a density difference of a 5% [21]. The density of calcium oxalate and cystine calculi had higher attenuation values than uric acid or xanthine calculi [22]. Newhouse et al. used NCCT to determine CT attenuation values to allow an accurate analysis of stone composition; uric acid and cystine calculi could be identified, but calcium-containing calculi such as struvite, brushite and oxalate could not be distinguished reliably from each other [23]. Thus identifying uric acid calculi became feasible by NCCT, but overlapping CT attenuation values posed problems in accurately determining different calcium calculi. Mostafavi proposed that the chemical composition of urinary calculi could be determined from the absolute CT values measured at 120 kV and the dualvoltage CT values measured at 80 and 120 kV (HU at 80 kV minus HU at 120 kV), the absolute CT value at 120 kV could identify the chemical composition of uric acid, struvite and calcium oxalate calculi, and the use of the dual-voltage CT value was able to differentiate calcium oxalate from brushite and struvite from cystine [24].

Later, in an in vitro study, Saw reported that the number of shock waves required to fragment the stone correlated with size (volume, weight, diameter) and helical CT attenuation values, and concluded that for calcium calculi, the number of shock waves to comminution was generally less than half the calculus CT attenuation value [25].

In an interesting in vivo study, Nakada compared the attenuation and the attenuation size ratio with the results of calculus analysis; there was a significant difference between uric acid calculi (344±152 HU), and calcium oxalate calculi (652±490 HU), and by using an
attenuation/size ratio threshold of > 80, the negative predictive value was 99% that a calculus would be predominantly calcium oxalate [26].

To date, few clinical studies have compared the density of calculi with the outcome of ESWL in vivo. Joseph, in a study of 30 patients, found that patients with calculi of <500 HU had complete clearance and required 2500 shock waves (median), while patients with calculi of 500–1000 HU had a clearance rate of 86% and required a median of 3390 shock waves, and patients with calculi of ≥1000 HU had a clearance rate of 55%, requiring a median of 7300 shock waves. These authors recommended that if the attenuation value of the calculus was >950 HU and 7500 shock waves had not achieved adequate fragmentation, percutaneous nephrolithotomy should be considered [27].

More recently, Pareek correlated calculus density with clearance in a study of 50 patients who were treated with a second-generation electrohydraulic lithotripter. They concluded that 36% of patients with residual calculi had a mean calculus density of ≥900 HU, compared with a mean of 500 HU in 74% of patients who had clearance [28]. However, they did not correlate the calculus density with fragmentation.

Narmada et al., when patients were categorised by calculus density, 80% with calculi of ≤750 HU needed three or fewer ESWL sessions and 88% had complete clearance. Conversely, of patients with calculi of >750 HU, 72% required three or more sessions for complete clearance. The best outcome was in patients with stone diameters of ≤1.1 cm and a density of >750 HU; 35% needed three or fewer sessions and the clearance rate was 90%. The worst outcome was in patients with a stone of >750 HU and diameter of >1.1 cm, 23 (77%) of these patients needed three or more sessions and the clearance rate was only 60% [18].
VII. Conclusions

- Insufficient daily fluid intake proved to be a significant risk factor in the occurrence of urinary calculi, for 71% of women and 30% of men (p <0.001).

- CT scan is a noninvasive method and performed before SWL can help to determine stone density and thus its fragility and treatment outcome.

- Knowledge of stone density could help in the planning of alternative treatments for patients with a poor prognosis, increasing SWL efficiency, reducing treatment costs, especially in patients with stone density higher than 1000 HU.

- A stone with density <500 HU and a size <16 mm, has a 100% chance of being resolved by SWL in 1.2 ± 0.5 sessions. Patients with stone density more than 1000 HU and size bigger than 10 mm, have “stone-free” rates of 22.2% in 3.6 ± 1.1 sessions.

- We found the threshold, below which most stones are uric acid, of 548 HU with a sensitivity of 97.9% (p<0.001).

- A density threshold of 852 HU is the best threshold for the identification of calcium oxalate calculi, with a sensitivity of 99.02% (p<0.001).

- A density of 945 HU is a threshold below which SWL is very effective, 85.35% of them being successfully. Any patient with a stone density exceeding 945 HU has 37.7% chances to succeed fragmentation by ESWL (p<0.001).

- For patients presenting calculi with density greater than 1194 HU, SWL should be contraindicated and therefore, the patient should be treated by PNL or laparoscopic surgery.

- Stone size greatly influences SWL outcome, but stone density has a much greater impact on the outcome than size.

- Preventive measures can be taken to reduce side effects. Modern lithotripters are user friendly, treatment is only moderately painful, but selecting and optimizing patient treatment protocols are needed to maximize "stone-free" rates and to minimize the side effects.
VIII. References