“CAROL DAVILA” UNIVERSITY OF MEDICINE AND PHARMACY

BUCHAREST

DOCTORAL SCHOOL

MEDICINE FIELD

PHD THESIS
SUMMARY

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2022

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CONTRIBUTION OF RADIO-IMAGING EVALUATIONS IN THE ASSESSMENT OF RENAL AND URINARY SYSTEM MALFORMATIONS: FROM SIMPLE TO COMPLEX

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CONTENT

The fundamental problem

Renal and urinary system malformations represent an important segment of pathology which encompasses all renal and urinary genesis defects like alterations in number, form, size and position, obstructive and non-obstructive, aplastic and dysplastic (including the cystic type), additional and non-additional, that come alone or are associated with other renal and urinary/non-renal and urinary congenital anomalies in syndromes that globally affect the renal and urinary system. This type of pathology is particularly important in the pediatric population and their correct investigation and monitoring is of major importance in the long-term prognosis and predictability of progression to CKD.

The sheer diversity of pathological entities included in CAKUT (congenital abnormalities of the kidney and urinary tract) requires the adaptation of imaging techniques and the use of combinations of radio imaging methods to meet advanced diagnostic requirements specific to complex malformations.

The primary motivation behind this thesis was to redact a piece of work that is intended to be a useful working tool for both radiologists (especially those less experienced in imaging assessment of children) and uronephrology practitioners. The ultimate goal is the avoidance of needless or excessive irradiation of the population most at risk and to establish a diagnosis as early as possible. Achieving this would allow for a more adequate treatment as a prerequisite of the follow-up of the associated kidney disfunction, avoiding reaching the point of CKD, which might require, sooner or later, radical surgical solutions i.e. nephrectomy or kidney transplant.

Working hypothesis and general objectives

CAKUT represents the most common malformations that we see in pediatric patients.

General objectives of the thesis were:

- the optimization and standardization of diagnostic protocols by increasing efficiency and reducing the irradiation dose;

- stating some clear indications for investigations that would regulate access to medical imaging, but also to counteract the excess of imaging investigations, especially of the ionizing type, occasionally seen in children with CAKUT;

- smoothing, improving and standardization of the methods of radio-imaging investigations with the purpose of establishing a complete and accurate diagnosis;

- establishing criteria for the imaging follow-up of these malformations by observing the clinical impact and the clinical and biological correlations;

- identifying of correlations between the different types of examinations by taking into account the advantages and limitations of each one of them, but also between the different imaging sequences and the functional factors with prognostic purpose;

- clustering the lesional entities on malformative categories, establishing of the main associated lesions that afflict the renal and urinary system as well as the other organs and systems and also fitting them into syndromes;

- classification and stratification of the malformative lesions of the renal and urinary system in risk categories for progression towards CKD;

- the development of diagnostic algorithms for positive and differential diagnosis for each malformation category, but in particular for the malformative associations that require combinations of imaging techniques;

- the identification of negative prognostic factors for the progression to CKD.

General methodology of the research

The extreme polymorphism of the malformative renal and urinary pathology, as well as the relatively frequent presence of lesion associations that turns them into complex malformations has resulted in a bushy database that encompasses numerous lesional entities, with extremely different weight in terms of number of cases.

1039 patients were included in the general database. All subjects studied were patients admitted to the Fundeni Clinical Institute, in whom imaging investigations detected, unexpectedly or not, renal or urinary malformative pathology. The storage of the acquired images was done in the PACS system of the Laboratory of Medical Imaging and Interventional Radiology.

The classic *CTU (CT Urography)* examination applicable to the adult patients was realized according to the following protocol:

- unenhanced phase;
- corticomedullary phase - performed with bolus tracking;
- nephrographic phase - obtained at approximately 90 seconds from injection;
- excretory phase - obtained at approximately 5 minutes from injection;

- optionally - a delayed phase, which is useful in urinary tract obstruction, obtained in approximately 1 h from injection.

CTU examination applicable to children with CAKUT is further explained in study 1.

The classic Uro-MRI examination performed in our clinic encompasses the following phases:

- Ax T2 fs;
- Ax T2;
- Sag/Cor T2 Short TE;
- Cor T2 Long TE;
- Cor SS-FSE;
- Ax ± Cor DWI;
- Unenhanced Uro-MRI Cor T1;
- Cor T1+ IV contrast - dynamic injection 7-10 min ± delayed phase;
- Ax T1 In/Out-of-Phase (optional).

Chapter summary

This paper is divided into two parts: "Current state of knowledge" and "Personal contributions".

In "**Current state of knowledge**" I have outlined information about the anatomy of the renal and urinary tract, the epidemiology of the reno-urinary malformations, the embryology, physiology and physiopathology of the reno-urinary tract. A classification of the malformations was made from various perspectives, the CAKUT embryological classification being the one that was chosen. The renal and urinary malformative associations grouped into diseases and syndromes were reviewed. In the last chapter of the general part a systematic review of the most used imaging methods from the simplest ones (ultrasound, IV urography, cystography) to the more complex ones (CT, MRI), emphasing the recommended protocols for patients with CAKUT.

In the second part called "**Personal contributions**" I have made a retrospective, observational study of the entire database of 1039 patients, which is a representative cohort of patients with renal and urinary system malformations.

The *objective* of this first global study was to present the pathological entities investigated in statistical terms and to compare them with the literature. For the descriptive analysis of the patients of each malformative category we used the following parameters:

- age, for which the average was determined, standard deviation (S.D), the median, the difference between the quartile of 75 and that of 25 (InterQuartileRange = IQR), the minimum, the maximum and the difference between them (distribution range), the skewness (deviation from the symmetry of the distribution, the value for the symmetric distribution being 0), graphic histograms (to identify the form of distribution) and boxplots (to identify extreme values - unusually low/high);

- sex of the patient for which the relative and absolute frequencies were determined and graphic barplots were used;

- imaging methods by which the diagnosis was established (CT/MRI/ultrasound etc.) for which the relative and absolute frequencies were calculated and graphic barplots were used.

The previous statistical study was complemented by 4 other studies that considered hypotheses with the main aim of improving diagnosis. Emphasis has been placed on certain segments of malformative pathology with the potential to progress to CKD. Depending on the working hypothesis considered, various lesional entities or imaging protocols were studied.

The first study had as a working hypothesis that the complete diagnosis of some reno-urinary malformations requires CT examination but that the protocol used is not optimal and could be adjusted for the lowest possible irradiation. This was realized by comparatively studying imaging diagnostic protocols in order to choose the optimal variant as a diagnostic-irradiation ratio without significantly losing the image quality and without making a compromise to the descriptive diagnostic information.

Under these conditions, the specific objectives of study 1 were:

- comparison of irradiation doses obtained by various CT examination protocols, as a result of exposure of pediatric patients to X-rays by various investigation protocols;

- comparison of the diagnostic accuracy of the used protocols;

- optimization of CT diagnostic protocols applicable to CAKUT;

- the establishment of specific indication to each protocol as a component of radioprotection.

We considered 3 groups of patients: *a first group* in which SBCT examination was performed, most patients being investigated for malformative reno-urinary pathology, *a second group* in which CTU examination was performed and *a last group* of patients in which abdomen and pelvic CT examination was performed for a diverse but non-urinary pathology. Patients included in the groups had a single CT examination which was either

SBCT or CTU with two enhanced phases or abdominopelvic CT with 3 enhanced phases. In some of the patients investigated by the split-bolus protocol, the examination was completed with a late excretory phase in order to adequately opacify the excretory pathways and confirm / refute the obstructive pathology and this turned the SBCT protocol into a two-phase CTU examination allowing the comparison of irradiation doses by the two protocols in the same patient. Irradiation was compared in patients with 2 or 3 post-contrast phases extracting from the irradiation dose of the multi-phase examination, the irradiation dose of the exploration with fewer phases.

Inclusion criteria for group 1 (the prospectively investigated group by SBCT) were:

- patients who have been previously investigated by ultrasound and had diagnostic uncertainties;

- patients with congenital urinary obstruction, potentially surgical, in whom a complete lesion assessment of both the obstructive lesion and the associated lesions was requested;

- patients with acute urinary symptoms such as renal colic/acute pyelonephritis on a malformative background in which ultrasound was negative for an acute pathology.

The *SBCT protocol* used consists in performing a single scanogram (frontal scanogram), an unenhanced phase and a single contrast-enhanced phase, with simultaneous opacification of the renal parenchyma and excretory tract. An 80-100k kV was used to reduce the radiation dose, especially in children weighing less than 40 kg. All pediatric examinations benefited from AEC (automatic exposure control). In SBCT, the injected iodinated contrast had a concentration of 300-370 mg I/ml, in an amount of 1.5 ml/Kgc and with a flow rate of approx. 1-2 ml/kgc [1]. The contrast was administered in fractions, in two stages, in each stage being administered 50% of the amount of contrast. The second stage of the injection was performed 420 seconds after the first stage or more (approx. 900 seconds) in cases where the previous ultrasound revealed moderate/severe obstruction of the excretory tract (Diagram 1).

DIAGRAM 1

SPLIT-BOLUS PROTOCOL

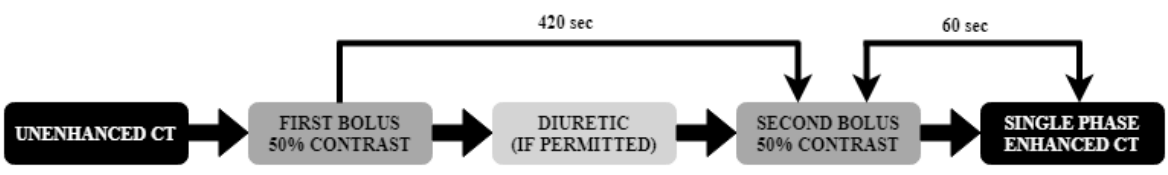

Chart 1. SBCT protocol

In addition to image quality and diagnostic accuracy (Figure 1), the presence of renal excretion (especially in the case of excretory tract ectasia) was studied, their degree of opacification and the presence of contrast in the ureter and bladder were also studied. In order to obtain a degree of standardization within the SBCT protocol, a score was assigned for the opacification of each segment of the excretory tract, score 0 representing absent opacification (unopacified/collapsed ureter) and score 4 representing complete opacification.

CTU examination performed for the second group included an unenhanced phase, a contrast - enhanced phase in intermediate time performed at approx. 60 seconds after injection and an excretory phase performed at approx. 420 seconds post-injection.

The typical abdominopelvic CT examination applicable to group no. 3 consisted of an unenhanced phase and 3 contrast-enhanced phases (an arterial phase performed at about 30 seconds after injection, a venous phase performed at about 45 seconds after the arterial phase and a parenchymal phase at approx. 180 seconds after injection).

All radiation doses were reported in mGy*cm.

In order to better appreciate the usefulness of SBCT in reducing children's irradiation and in diagnosing malformative and non-malformative reno-urinary pathology, two other studies were performed analyzing the same parameters as the first study but between different groups.

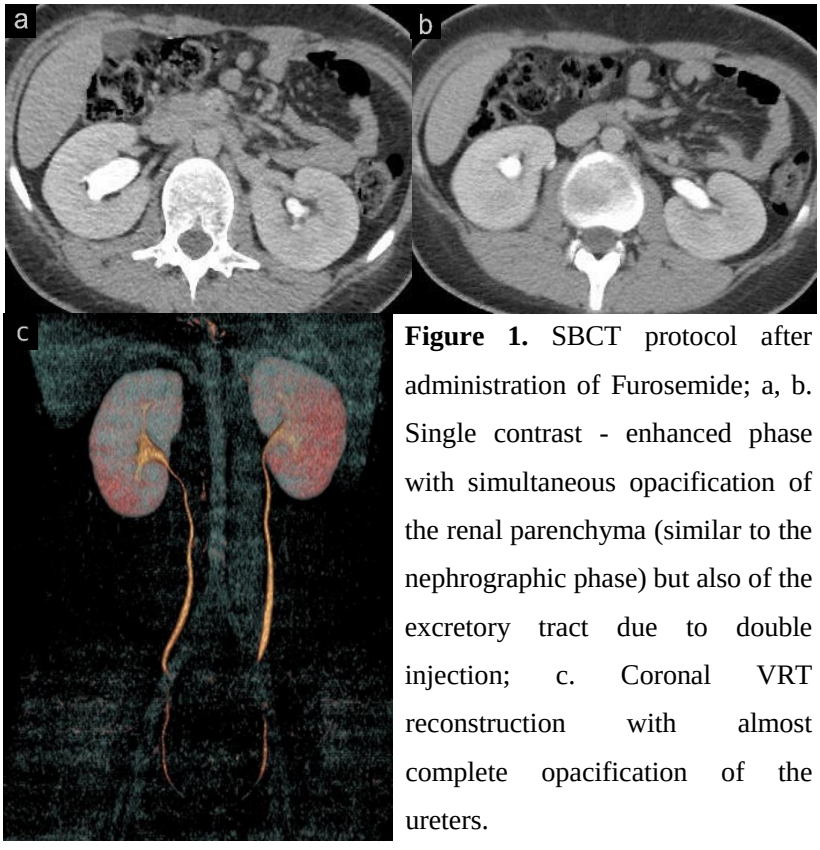

Figure 1. SBCT protocol after administration of Furosemide; a, b. Single contrast - enhanced phase with simultaneous opacification of the renal parenchyma (similar to the nephrographic phase) but also of the excretory tract due to double injection; c. Coronal VRT reconstruction with almost complete opacification of the ureters.

The first substudy was a retrospective, observational, non-randomized one between the groups of patients investigated through 2 phases CTU and patients investigated through 3 phases CTU, prior to the implementation of SBCT protocol.

The second sub-study is also a retrospective, observational, non-randomized one on a sample of 25 patients where DLP was compared between a 2 contrast - enhanced abdominopelvic CT versus a 3 contrast-enhanced abdominopelvic CT performed for non-urinary pathology.

The *results* obtained were initially statistically analyzed.

The most important result was the radiation dose (Table 1).

Dose	SBCT	2 phases CTU
Average ± S.D.	**400.48 ± 202.03**	**604.65 ± 302.00**
Median (IQR)	**360.00 (145.00)**	**534.00 (208.50)**
Min la Max	**104 la 1072**	**152 la 1606**

Table 1. Comparison between SBCT versus 2 phases CTU radiation doses.

1. Statistically significant differences ($p < 0.01$) were found between SBCT dose and 2-phases CTU proportional dose through a bidirectional paired T test because the design is with correlated variables (dose measurements in the same patient), as shown in Figure 2.

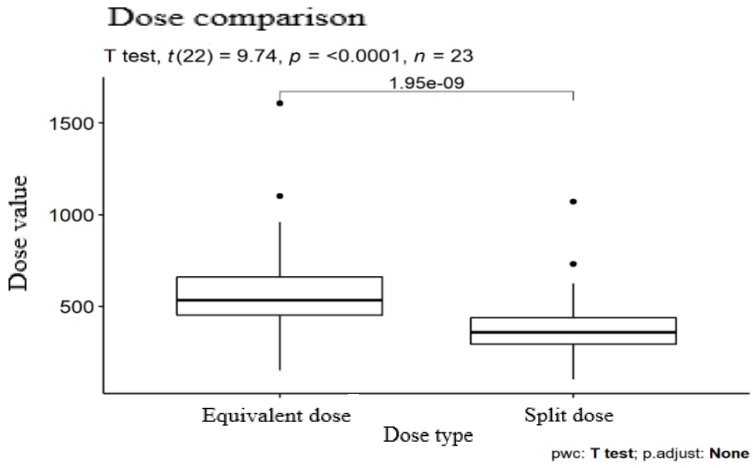

Figure 2. Dose comparison in CT protocol (SBCT versus CTU).

2. The age of the patients influences the differences between the 2 doses (given the fact that almost all patients in the SBCT protocol are under 18 years old). This was proven by an ANCOVA one-way repeated measures test (unidirectional covariance analysis) in which the dependent variable is the measured/estimated dose value, the factor is the dose type and the covariate is the age category of the patient.

3. Regarding the first and second sub-studies, the same bidirectional paired T test was applied and it was found that there were statistically significant differences ($p<0.01$) between radiation doses by 2 phases CTU and 3 phases CTU, as well as between radiation doses of the patients investigated by classical CT protocol with 2 enhanced phases, respectively 3 enhanced phases CT.

Based on the results of study 1, *the discussions* are presented below.

Although the SBCT examination is a low-radiative examination, the issue of eliminating the unenhanced phase from SBCT/CTU examinations is increasingly being raised. A compromise solution would be to eliminate the unenhanced phase from the protocol in the case of ultrasound nondilated kidneys, without ultrasound-detectable lithiasis and in the absence of renal colic symptoms. It should be mentioned that the elimination of the native phase is a desideratum that in the future could be overcome in Romania by using digital subtraction. This method is applicable on new generation dual-energy CTs via GSI [2].

Another way to solve radiation dose versus diagnostic accuracy dilemma remains LDCT examination applied in the unenhanced phase with a strict role in the detection of lithiasis and calcifications but with an increased image noise [3].

The last but probably the most important goal of the split-bolus protocol is to *reduce radiation dose*. Given that the CT examination followed a rigorous ultrasound scan(s) that carefully assessed the renal parenchyma, there were no cases in which expansive CT lesions were detected that could not be characterized as CT due to the fact that a single enhanced acquisition was made. In these circumstances, the protocol has a high diagnostic accuracy and has achieved its goal of fully diagnosing malformations using a low dose of X-rays. In the case of ultrasound suspicion of expansive renal lesions, however, an SBCT examination is not indicated, but CTU protocols in two enhanced phases that allow the evaluation of the kidney both morphologically and functionally.

In terms of radiation doses, the reduction is significant (overall reduction of approximately 30%) without significantly losing image quality.

Advantages of SBCT examination:

- reduction of radiation doses compared to classical CTU examination;
- complete diagnosis of most malformative-obstructive diseases;
- reduced investigation time compared to MRU (MR-Urography) examination.

Disadvantages/limitations of SBCT:

- incomplete investigation of congenital vascular pathology (for example renal artery stenosis) or tumors associated with urinary tract malformations;
- uses X-rays (low but still present irradiation);
- reduced/no usefulness in the investigation of vesicoureteral reflux or congenital urethral pathology;
- although the delay between the two injections is long enough, sometimes (in severe obstructions) the opacification of the excretory tract may be suboptimal;
- due to the single enhanced acquisition, it does not reliably quantify the small delays of renal excretion.

The main *conclusions* of the study:

1. *SBCT* is the best CT protocol for the diagnosis of upper urinary tract malformations in children.
2. The protocol has a very good sensitivity and diagnostic accuracy in the detection of CAKUT, the main indication being the symptomatic/complicated obstructive malformations.
3. The radiation dose is reduced by approx. 30% compared to the commonly used protocol.
4. Although there are clear advantages over MRI in terms of accessibility, examination time and cost of investigation, MRI retains supremacy in cases associated with congenital pelvic abnormalities (ectopic ureteral implants, genital abnormalities, subvesical abnormalities).

Study 2

The working hypothesis underlying this study is that fibrotic changes in the renal parenchyma lead to a reduction in the size of the kidney and, more importantly, to changes in the diffusibility of water in the renal parenchyma.

The main objective of study 2 is to establish the *correlation* between the *degree of renal insufficiency* (as a result of fibrotic impairment) and the *value of the apparent diffusion coefficient (ADC*).

A retrospective, observational, non-randomized study was performed on a sample of 110 patients, children and adults, investigated by MRI between January 2015 and March 2021 at the Fundeni Clinical Institute in Bucharest, divided into 4 groups:

- group A - 33 patients with CAKUT and renal dysfunction up to CKD (CKD stages G2-G5);

- group B - 18 patients with CAKUT but without renal dysfunction (GFR over 90 ml/min/1.73 sqm);

- group C - 27 patients without CAKUT and without renal dysfunction;

- group D - 32 patients without CAKUT (mostly with oncological pathology) but with renal dysfunction (IRC stages G2 - G5);

In the study groups, the DWI acquisition was performed in at least one plan. The ADC map was automatically generated and studied in detail. Three ADC values were measured for each kidney (at the upper, middle and lower renal poles), and then an arithmetic mean of the ADC values for each kidney was made. The measurement was done manually in the form of an ROI of approx. 1 cm^2 placed in the renal parenchyma comprising both portions of the cortex and medulla.

The mean ADC value was calculated as the average of the ADC values for the two kidneys.

The *results* of study 2 are summarized below:

1. Patients in groups A and D (those with IRC stages G2-G5) had high serum creatinine values which resulted in low RFG values. Because most patients with suboptimal renal function were classified as G2, the relatively small number of patients with patented CKD (G3, G4, and G5 stages) did not allow a reliable statistical comparison of each category of CKD but only of the patient group with lower renal function (G2) than in patients with actual CKD (G3 - G5 stages).

2. Statistically significant differences were found between groups A and B, A and C, A and D, B and D, C and D, differences reflected in Figure 3 and Table 2.

3. The ANOVA analysis performed for the differences between the ADC values reveals that there are differences with statistical significance between the lots ($p < 0.01$), this was complemented by a post-hoc ANOVA procedure using Tukey's multiple testing correction (a less conservative correction than Bonferroni).

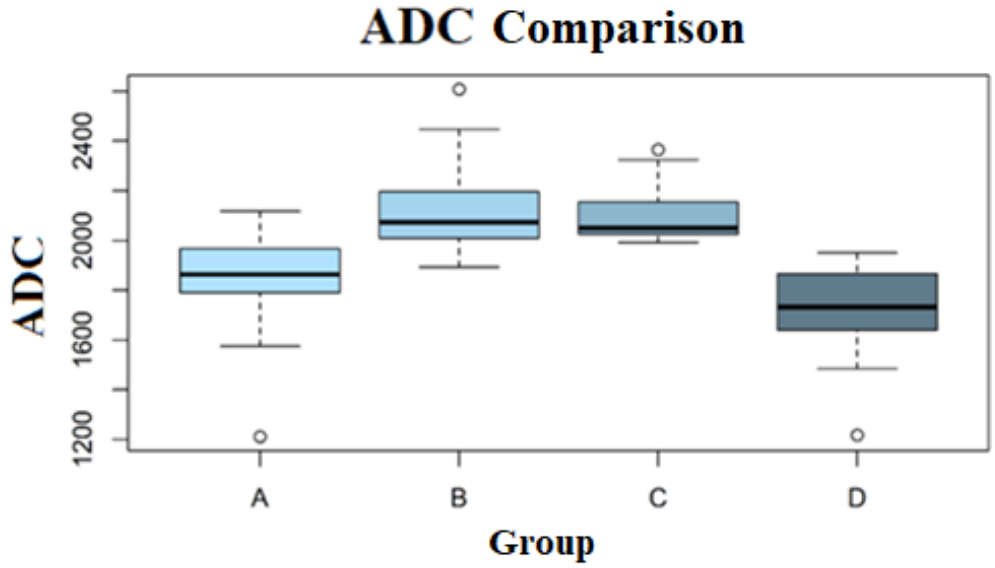

Figure 3. Comparison of ADC values in the 4 study groups.

Average group A	Average group 2	Average group 3	Average group D
1849.67	2133.34	2099.24	1726.85

Table 2. Average ADC values in the 4 study groups.

4. Since relatively small differences were found between the ADC values in groups A and D, an ANCOVA analysis was performed using age as a covariate and it was found that age did not induce statistically significant effects between groups A and D (adjusted p value > 0,05).

5. Based on the ANCOVA statistical analysis using blood creatinine/urea or GFR as covariates, it was found that all these variables induce statistically significant effects ($p < 0.05$) in the groups studied, with ADC values being influenced by these parameters.

Discussions resulting from the study 2 are detailed in the following section.

The major advantage of the DWI sequence is that, although it is part of functional MRI techniques, *it does not require the administration of paramagnetic contrast agent*, making it applicable to CKD patients in whom contrast administration would be limited/contraindicated. In patients with CAKUT, mainly the interstitial compartment is affected [4], which implies a more obvious functional alteration at higher b values through functional restriction of true diffusion and less tissue perfusion. The degree of disease severity should be higher in case of obstructive malformations as in pyelo-ureteral junction syndrome or vesicoureteral reflux, with the caveat that, in severe obstructive impairments

associating grade IV HN/UHN, the sequence becomes unusable because there is no longer functional renal parenchyma. The same situation is found in case of the sclero-atrophic kidneys but the sequence may be extrapolated to the transplanted kidneys.

The fact that patients with congenital malformations with CKD (group A) had statistically significantly higher ADC values than group D patients (patients with CKD of other causes) in the analysis without covariate, is due to the older age of group D patients.

The fact that the patients in group A had statistically significantly lower values of ADC compared to group C (the normal one) correlates positively with the value of GFR, the lower values belonging to patients with CKD. A significant inverse correlation between ADC values and serum creatinine (and urea) values quantified by Pearson's correlation coefficient and a significant linear correlation between ADC values and eGFR was demonstrated. Regarding the evolution of ADC values in relation to CKD grade, a decreasing trend of ADC values with increasing CKD stage was observed [4, 5, 6].

However, there are still major discrepancies in the ADC values assigned to each category of CKD. The functional implications of the ADC-GFR-CKD correlation are, however, the most important because ADC values must be established as an imaging biomarker, beyond which functional impairment is irreversible.

The following *conclusions* can be drawn from this study:

1. DWI sequence can be a valuable tool in MRI evaluation of patients with CKD (including malformations) without the administration of a contrast agent.

2. Measurements accuracy is however impaired in patients with significantly thinner/absent renal parenchyma, which reduces patients eligibility.

3. The method must be supported by other sequences to demonstrate / quantify renal fibrosis.

Study 3

The working hypothesis underlying this study was that some of the renal and urinary tract malformations belong to a high-risk group for deterioration of renal function and progression to CKD. This requires the discovery of new methods of investigation or new applications of those already known, preferably non-invasive, non-irradiative and without use of paramagnetic contrast.

T1 mapping sequences are new MRI sequences, commonly used in heart imaging but recently expanded in renal imaging. They are based on the classical T1 sequence and are

currently being evaluated in renal imaging, with the expectation of being able to characterize the renal parenchyma [7, 8].

There are several technical variants of T1 mapping. MOLLI sequences are classic inversion-recovery sequences used primarily in cardiac MRI. The alternative to inversion-recovery sequences is saturation-recovery sequences.

The SMART1 sequence (Saturation Method using Adaptive Recovery Time) is a type of T1 sequence that is part of the saturation-recovery sequences being, in essence, also a GE sequence (gradient echo) with multiple gradient echoes and flip-angles.

The *specific objectives* of the study are:

- assessing the reliability of the SMART1 sequence in renal imaging;

- identification of imaging-biological correlations between T1 values and parameters that reveal the deterioration of renal function;

- establishing the contribution of the T1mapping sequence in quantifying the degree of renal fibrosis and the utility to introduce this sequence in the standard MRU investigation protocol of patients with renal dysfunction of malformative and non-malformative cause.

The novelty of the technique is that there are so far no published studies on the use of this sequence for the study of renal parenchyma and there are very few studies on the use of this sequence in the quantification of myocardial fibrosis.

This is a pilot study, prospective, observational, non-randomized, in which both pediatric and adult patients of both sexes have been enrolled so far.

The study included 49 preliminary patients divided into two groups:

- a group of patients with CKD, most of them due to reno-urinary malformations;

- a group of patients without CKD, investigated for a pathology other than renal, most of them with neoplastic pathology.

The *results* of the study are presented in the following paragraphs.

1. T1 mapping maps measured T1 values expressed in milliseconds (ms). The black-and-white maps were complemented by color maps obtained through the NIH (National Institutes of Health) application in the MAC mini post-processing console that quantifies T1 values on color codes to facilitate interpretation (Figure 5, Figure 6).

2. For most patients the sequence was acquired before injection but in some patients the sequence was also performed after contrast injection to verify its accuracy.

3. The T1 mapping values obtained are significantly higher than those reported in the literature, obtaining mean values of 1870 ms for patients with CKD and 1630 ms for patients without CKD (Figure 4). This is explained by the fact that the SMART1 sequence measures

real T1, which is higher than the apparent, uncorrected one, confirming the conclusions of the study by Matsumoto et al. [13].

4. Because the sample size was suboptimal for the application of the central limit theorem in statistics (a theorem that would have allowed the use of parametric tests regardless of the presence/absence of outliers but requiring batches of at least 50 patients in each batch), the central tendency of the two was quantified using medians rather than arithmetic means (the median being more robust to the existence of outliers). For this reason, the inference test used was two-way Wilcoxon Rank Sum, a test that measures the difference in location between two independent distributions, this difference was measured using the two (pseudo) medians.

5. In order to investigate the possible existence of the "confounding" effect (error factor) of age on T1 values, the ANCOVA analysis could not be used but its non-parametric version.

6. The degree of statistical significance α was 0.05 (5%), so p values below 0.05 were considered statistically significant.

Average T1	Group A (N=26)	Group B (N=23)	Global (N=49)
Average (SD)	**1870 (309)**	**1630 (309)**	**1760 (330)**
Median [Min, Max]	**1880 [1210, 2500]**	**1710 [876, 1950]**	**1830 [876, 2500]**

Table 3. T1 sequence analysis for study patients (calculated as the average of the T1 values obtained for both kidneys).

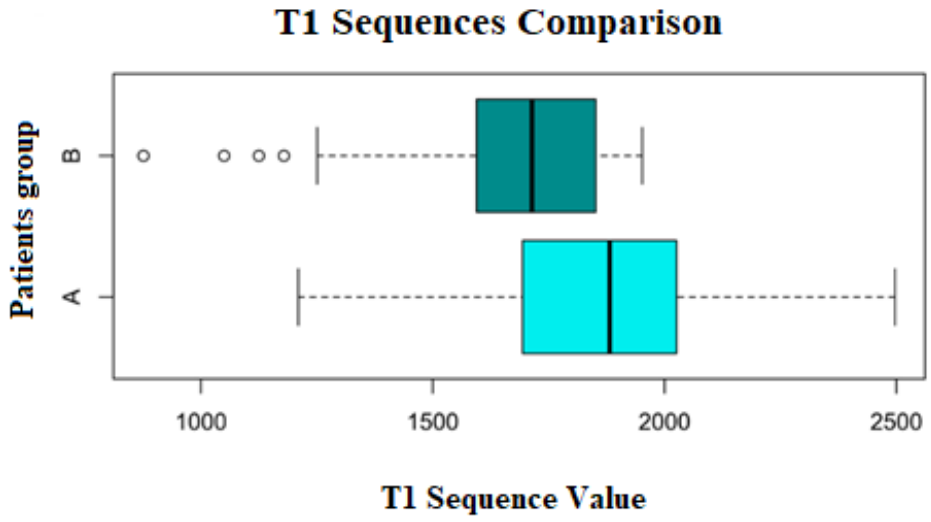

Figure 4. T1 sequence values for the two study groups.

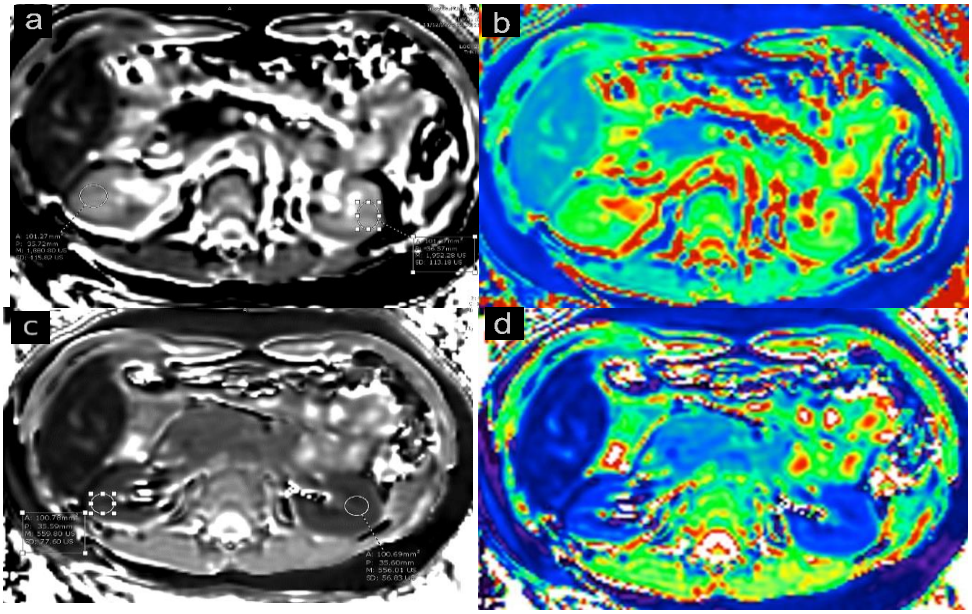

Figure 5. SMART1 sequence on normal kidneys: a, c. unenhanced T1 mapping with mean T1 values of 1916 ms and enhanced T1 mapping with mean T1 values of 558 ms (c); b, d. T1 color map obtained by unenhanced (b) and enhanced (d) NIH postprocessing.

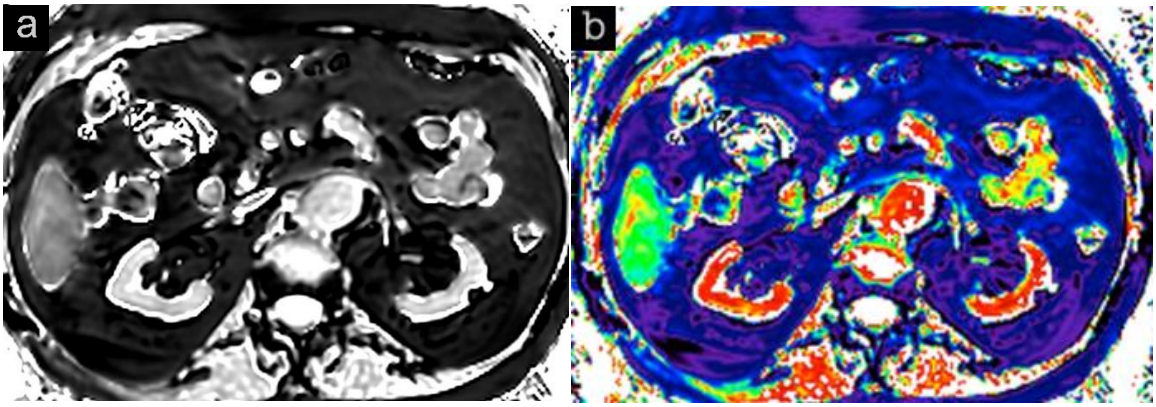

Figure 6. Unenhanced SMART1 sequence in a patient with G5 stage CKD; a. T1 mapping- high T1 values - average T1 values on both kidneys of 2003 ms; b. NIH postprocessing.

Discussions on T1 mapping sequence are detailed below

One of the theoretical advantages of SMART sequences is the reduced acquisition time, which should reduce motion artifacts [9] However, in practice, we found the fairly frequent presence of some artifacts, most likely representing magnetic susceptibility artifacts, more common in the case of gradient-echo sequences.

The biggest advantage of this sequence compared to the MOLLI/ShMOLLI sequence is that it measures true T1 and not apparent T1 because, unlike MOLLI/ShMOLLI sequences, this sequence is not influenced by T2. This should ensure better accuracy and stability in parenchymal analysis, including kidney [10]. Due to the fact that it is a single-

shot sequence, it is not significantly influenced by the image parameters and it has the additional advantage that it does not require post-processing as it is automatically generated [10].

The sequence was credited with a high dynamic range and a high signal-to-noise ratio (SNR) compared to the classic T1 sequences [9], which was confirmed on the studied patients. The presence of these artifacts would have been a rather important limitation in cardiac imaging but, despite the artifacts, the sequences are interpretable in renal imaging.

The fibrotic changes that occur in CKD cause T1 alteration at the cortical level, leading to cortical T1 increase and, consequently, global T1 increase [11, 12]. However, given that in most patients with advanced CKD cortico-medullary differentiation is lost, separate cortico-medullary measurements are proving unfeasible for this pathology, so the only applicable method is to perform measurements at the renal parenchymal level in the form of ROIs encompassing both cortical and medullary.

The negative correlation between T1 values and GFR values, similar to the positive correlation between fibrosis and T1 values, should be used to detect subclinical stages of fibrosis [14]. Another practical applicability of T1 maps could be their use as a predictor of renal graft function.

Almost non-existent studies in the literature on the use of the SMART1 sequence in characterizing renal parenchyma do not allow reliable comparisons. The only comparisons that can be made are with similar sequences (MOLLI, SASHA or SAPHIRE type) but not identical in production mechanism or physical parameters.

Although most of the studies generally had a relatively small number of patients, they all concluded that there was a statistically significant correlation between the degree of CKD and T1 values [11, 14, 15]. The T1 values obtained at the level of the kidneys vary a lot depending on the pathology and the sequence.

However, the values obtained in the present study were quite heterogeneous, varying within fairly broad limits and there were some outliers that did not fit into these trends, i.e. overlaps of the ranges of values assigned to each stage of CKD. However, SMART1 sequence could have a significant predictive value in an unenhanced MRU protocol which should include both morphological sequences (Cor T2 Long TE, Cor T1) and especially functional sequences such as DWI, T1 mapping, T2 mapping, ASL, BOLD in order to quantify the degree of renal damage and the potential for reversibility through the presence of an inflammatory/edematous component associated with the fibrotic component.

However, the examination must be adjusted according to the pathology.

The MRU protocol for patients with malformative and non-malformative kidney disease that causes high-stage CKD (stages 3-5) should include the following sequences for which there are firm recommendations and consensus from experts:

- Cor T2 Long TE;
- Axial T2;
- Axial DWI;
- Axial T1 mapping;
- Axial In/Out of phase;
- Unenhanced 3D T1 (coronal or axial);
- ASL/BOLD [16].

As *conclusions* of the study, we can conclude that:

1. *SMART1 is an innovative sequence* that, in a more complex MRI assessment protocol, can bring important information about the condition of the renal parenchyma through a non-invasive and non-irradiating examination.

2. There is a preliminary positive correlation between the degree of CRI and T1 mapping values which needs to be confirmed and further investigated by further correlations between T1 mapping values, T2 mapping values, DWI and MR/US elastography.

Study 4

The working hypothesis underlying this latest study was that there are in practice difficulties in the differential diagnosis of unilateral renal agenesis (which we will refer to because bilateral agenesis is incompatible with life) but also errors in the diagnosis of existing malformations on congenital solitary kidney (CSK) due to their polymorphism. The study comprises several sub-studies that have renal agenesis (RA) in common, each representing a specific study objective.

The *specific objectives* of the study were the following:

- establishing the reliability of ultrasound as the only method of diagnosis and monitoring of RA;
- analysis of the compensatory dimensional increase of the CSK compared to the normal kidney and the establishment of its possible prognostic role in renal functional impairment over the course of life;

- establishing the reliability of CT quantification of renal function based on a standardized formula compared to measurements based on classical formulas (MDRD, CKD-EPI, Bedside-Schwartz);

- analysis of lesional associations and creation of a complete algorithm (positive and differential) for diagnosis but also for monitoring both RA and complex malformations frequently associated with it.

The first group of study included patients investigated strictly by ultrasound for the diagnosis of RA. There were 23 pediatric patients investigated in the pediatric ultrasound department of Fundeni Clinical Institute between January 1st, 2015 - December 31st, 2020, whose ultrasound images were stored in the database and allowed further analysis.

The elements of *ultrasound diagnosis* taken into account were:

- absence of kidney in the renal fossa or in the rest of the abdomen/pelvis;

- increased compensatory size of the contralateral kidney;

- ratio over 0.9 between DAP (antero-posterior diameter) and DT (transverse diameter) of CSK;

- possible minimal-slight distension of the CSK pelvis;

- absence of Doppler visualization of the renal artery and vein on the affected side, with generally normal flow in the vascular pedicle of the single kidney.

To achieve these goals, both DAP, DT and DL of the CSK were measured.

The second study group included 20 patients with renal agenesis in whom *the degree of compensatory hypertrophy of the CSK* was measured. Patients with CT scans showing CSK but with a kidney larger than normal that age and sex were included in the study. Patients whose kidneys were small due to sclero-atrophy of the CSK, secondary to repeated pyelonephritis (probably by severe but uninvestigated VUR in the history) were excluded from the group. Also, a number of 6 patients with RA and compensatory dimensional increase but investigated by MRI were not included in the group. This was done so as not to alter the homogeneity of the study group.

The renal volume was measured by the disc summation method, which is a semi-automated method whereby the renal outline was manually traced on each slice of the acquisition, then, automatically, the slices were composited reconstructing the single kidney volume. This more accurate method than the classical ellipsoid method allowed for more correct volume estimation by excluding the hilum and renal sinus from the measurement ROI [17].

The degree of renal hypertrophy was estimated by relating the renal volume measured by CT examination and the mean renal volumes of normal kidneys reported in 3 studies in the literature (the percentage increase in renal volume was reported). The literature studies used for comparison were those conducted by Gong et al. [19], Cheong et al. [20] and Roseman et al. [21] who imaged large batches of patients with two kidneys by calculating normal renal volumes for both sexes and various age groups.

The third study group included 16 patients diagnosed by CT with renal agenesis, in whom GFR of the solitary kidney was estimated based on imaging examination using the Herts method [18]. Subsequently the estimated GFR value by the formula including the renal volume measured by CT was compared with the mean GFR calculated by the CKD-EPI and MDRD methods.

The calculation of e-GFR (estimated GFR) from sectional imaging examinations was done based on the formula GFR CUn = 70.77 - 0.444xV + 0.366xG - 0.200xVr - 37.317xCr in which GFR CUn represents the calculated unadjusted GFR, V represents age, G represents weight, Vr represents renal volume and Cr represents creatinine value [18]. Renal volumes were obtained by the same disc summation method used in the previous study group.

The group of patients related to *sub-study 4* was the whole group of agenesis (56 patients).

The results obtained are summarized below.

1. Regarding *the first objective of the study*, it was found that the dimensions of ultrasonographically assessed CSK were significantly larger compared to those of normal kidneys.

2. Regarding *sub-study 2* targeting *the degree of renal compensatory hypertrophy / hyperplasia* encountered in all investigated cases, a one-way ANOVA analysis for repeated measurements (ANOVA) was used to compare renal volumes, as the study design was with correlated variables. The analysis revealed that there are differences with statistical significance between all 4 values of the volumes (the 3 theoretical ones from the literature and the one measured by CT).

The following graph summarizes the analysis (* → $p < 0.05$, *** → $p < 0.001$, **** → $p < 0.0001$).

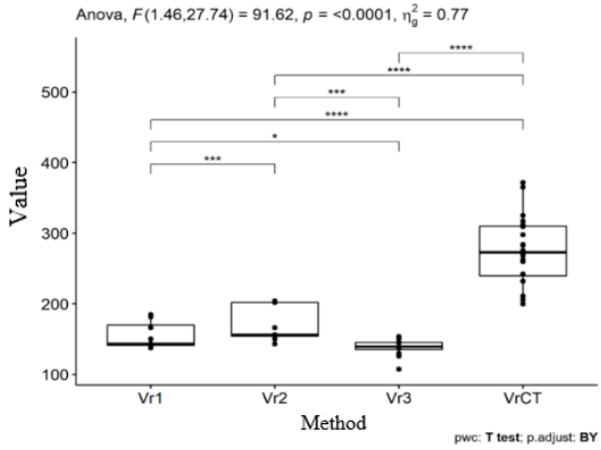

Figure 7. Comparison of measured renal volumes for RA versus normal volumes.

3. The Pearson's r correlation index between the degree of renal compensatory hypertrophy and RFG was 0.73, with a p-value = 0.0002, indicating a positive and statistically significant correlation between the two parameters. Given the situation in the group (with only 16 observations for which GFR could be calculated by CKD-EPI and MDRD), we compared the calculated GFR according to the Herts method with the mean GFR calculated by the CKD-EPI and MDRD methods.

GFR	Herts method	Average (CKD-EPI & MDRD)
Average ± S.D	**101.45 ± 11.64**	**88.00 ± 21.72**
Median (IQR)	**101.78 (9.58)**	**85.62 (17.80)**
Min. la Max.	**75.93 la 118.59**	**63.75 la 152.00**

Table 4. GFR comparative data.

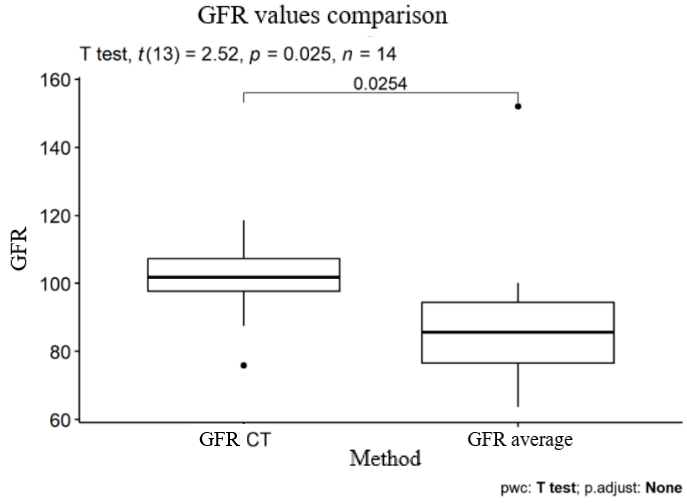

Figure 8. Comparison of GFR values calculated by CT versus classical methods.

4. The differences are statistically significant, $p < 0.05$, as shown in the previous graph (Figure 8).

5. Regarding RA-related anomalies, of the group of agenesis investigated, 29 patients (51.8%) had anomalies, these being renal and urinary anomalies on the RUC (16 cases - 28.6%), genital anomalies (13 cases - 23.2%) and vascular anomalies (2 cases - 3.6%), some combined.

Discussions regarding the study of renal agenesis are presented below.

The difficulties of differential diagnosis that we face especially in ultrasound lie in the fact that all the alternatives of differential diagnosis involve the existence of small kidneys, very difficult to detect sonographically. The biggest value in this approach has the dimensional increase of the solitary kidney. It seems that the sharpest increase is in LD, followed by APD and TD, leading to an increase in the APD/TD ratio [24, 25].

Ultrasound evaluation accurately highlights all these measurements. In these circumstances, *the ultrasound finding of a APD/TD ratio close to 1 (above 0.9)* is a reliable diagnostic element with excellent specificity for the positive diagnosis of RA.

Regarding the correlation between the GFR value calculated by CT (Herts method) and the GFR value calculated by classical formulas, significant differences were found between the values obtained by the two methods. Given that the GFR value calculated by classical formulas (CKD-EPI, MDRD or Bedside-Schwartz) is validated by time, we can conclude that the GFR calculated by CT evaluation method is not viable in its current form and requires more careful analysis and possible adjustments.

The presence of lesional associations exponentially increases the probability of complications occurrence and their severity. Essentially, it is not the RA itself that causes CKD but the potentially severely progressive urinary malformations in the CSK.

Among the associated urinary abnormalities we mention vesico-ureteric reflux (VUR), pyelo-ureteral or uretero-vesical junction obstruction, pyelo-ureteral duplication, ureterocele, posterior urethral valve, renal ectopia [22, 23], the most common associated anomaly being according to the literature VUR. Among the genital abnormalities, the most common are uterine anomalies, especially didelphys uterus and bicornuate uterus. [27].

Although many studies show that CSK preserves function in the long term, Sanna-Cerchi et al. looked at the time of onset of CKD in patients with RA and found that quite a large proportion of patients reach various degrees of CKD around the age of 30 which contradicts the perception of the "benign" progression of RA [26]. Westland et al. based on

a complex meta-analysis, concludes that approximately 10% of these patients reach CKD [22].

The best way to assess *the functional impact of CAKUT present on CSK* is to quantify the number of patients with CKD out of all patients with RA. In the study, out of the total number of patients, 28 were diagnosed with normal renal function (G1 KDIGO), 20 patients with mild renal dysfunction (G2) and 8 patients with patent CKD (3 patients with stage G3, 2 patients with stage G4 and 3 patients with stage G5).

Study 4 led to the following *conclusions*:

1. In the case of simple RA, diagnostic ultrasound examination following the above criteria is sufficient but in the case of CAKUT on CSK sectional imaging is required.

2. As an imaging method, MRU is preferable because it certainly excludes aplasia, ectopia and multicystic dysplasia and is the method of choice for the diagnosis of associated genital anomalies.

3. CTU remains indicated only if MRU is unavailable or contraindicated.

4. In the case of simple RA, ultrasound examination and laboratory analysis every 1 year are recommended as a monitoring method; in the case of RA associated with CAKUT on the solitary kidney, the associated abnormality must be monitored.

5. The positive correlation between renal compensatory hypertrophy and GFR can be used as a functional prognostic factor but the measurement of GFR based on CT examination has not proved viable in its current form.

Conclusions and personal contributions

The extent to which scientific objectives have been achieved

The main purpose of this thesis was to establish clear directions and precise standards for concrete and complete diagnosis of renal and urinary tract malformations by using the latest and most advanced imaging diagnostic methods. These standards have been achieved by developing imaging algorithms that cover the entire CAKUT spectrum, from the simplest to the associated/complex/syndromic ones. This was done after a detailed analysis of the pathological entities diagnosed radio-imaging in relation to functional aspects with a prognostic role.

Various malformative types identified by imaging in relation to morphological, clinical, paraclinical parameters were studied.

The contribution of each type of imaging examination in the diagnosis of various renal and urinary tract malformations has been affirmed or reiterated.

Negative prognostic factors have been identified and correlations have been established between various imaging examinations/sequences and prognostic functional factors.

Weaknesses of the examination protocols were identified and as well as ways to overcome them were identified.

The identification of patients with severe malformative pathology in advanced stages of CKD at the time of imaging diagnosis revealed diagnostic deficiencies, especially in conditions of poor symptomatology.

This analysis allowed stratification of CAKUT into risk groups according to the potential for renal impairment and progression to CKD.

This work aimed to identify malformative elements and associations that, in conjunction, negatively influence renal functional prognosis. Morphological-functional correlations were sought to explain the evolution of malformations in CAKUT

Socio-economic advantages and disadvantages

Regarding the technical and material basis necessary for the studies, we have benefited of equipment for high-performance diagnostic imaging, both CT and MRI examinations. The high-performance acquisitions and the various possibilities of post-processing allowed comparative studies which concerned both the reno-urinary malformations as a whole and also their components (for example renal agenesis, vascular malformations).

The possibility of analysis in CT acquisition of both radiation doses as a whole and of those broken down by each phase allowed comparative studies to be carried out in terms of radiation between various acquisition protocols, in order to implement them with a low-dose radiation imaging, as well as standard examination protocols for each type of pathology.

Acquisition of new innovative sequences for Romania useful in CAKUT diagnosis and monitoring was possible with the endowment of the hospital with 3T MRI equipment. Regarding the ultrasound equipment, this component was deficient because our ultrasound machine did not have high-performance software for contrast ultrasound, extremely necessary for performing sonocystography as an alternative to classical voiding cystourethrogram. This was a great disadvantage of this study. Also, I did not have any software for elastography, this being initially one of the CAKUT study objectives. From

those reasons, these studies remain as directions for further research, completing the studies carried out within this PhD.

Individual analysis of each patient from a very large study group that included over 1000 patients was also a major disadvantage that brings us back to our attention the need for large-scale implementation of standardized, structured results that would have allowed much easier access to diagnostic information and much more efficient data processing.

Limits of the study

The database taken as a whole was very generous with over 1000 patients which allowed a proper statistical interpretation but for some rare or very rare malformations, the number of patients was very small or even zero. There were malformative categories (e.g. bladder exstrophy, cloacal malformations, urethral valves) that benefited from surgery or perinatal endoscopic procedures or during infancy, later appearing in our service where they benefited only from postoperative monitoring.

There have been cases of adult patients discovered absolutely accidentally with malformative pathology, clinically silent although the kidney damage was severe, which reiterates the importance of mandatory medical examinations.

Some study groups were limited in number of patients, which did not allow a proper interpretation, sometimes affecting the statistical significance.

For example, in study 3, the late accessibility to the state-of-the-art imaging equipment needed for the study (3T MRI equipment) and the extremely limited time did not allow enough patients to be reached in the group, the study remaining open for further analysis.

Also, in the sub-studies related to study 4, the lower number of patients from each group did not allow to obtain data with obvious statistical relevance.

The dimensional reduction of the study groups was caused by the unavailability of some data/parameters necessary for a correct analysis. Although some patients had congenital diseases, they were diagnosed late, sometimes incidentally with urinary tract malformations. In some cases, this severely affected the patient's functional prognosis.

All patients were manually processed into the database and all measurements were made personally, in some situations not excluding potential unintentional errors, sometimes influenced by knowledge of the patient's diagnosis and evolution.

Unsolved issues

One of the main problems of this doctoral study is the absence of ultrasound software allowing more complex elastographic or contrast analysis (e.g. sonocystography) that could optimize diagnosis and allow to avoid irradiating imaging examinations especially in children. The purchase of such software will allow such studies on pediatric patients suspected/confirmed with CAKUT. In studies of renal agenesis, the discrepancy between GFR measured based of the Herts method and GFR measured by classical MDRD or CKD-EPI formulas is unclear, but significant differences between these measurements raise questions about the reliability of the method based on CT calculated volumes (Herts method). Although there are some assumptions, questions about the extent of the differences remain unclear.

The relatively small study group in the T1 mapping hypothesis, due to the impossibility of starting the analysis earlier, does not allow firm conclusions to be drawn about the statistical significance of the T1 values, requiring further study.

Directions in which scientific research should be continued

The role of the SBCT study was to establish CT investigations as basic investigations in the diagnosis of complex forms of CAKUT. Scientific research from this study should be continued in the following directions:

- conducting a comparative study of LDCT versus unenhanced CT without low-dose for the diagnosis of lithiasis/hydronephrotic complications;

- comparison by a randomized study of the diagnostic accuracy of the SBCT examination and single bolus CT examination with a single enhanced phase (excretory phase);

- comparison of radiation doses and diagnostic efficiency between CT examinations on conventional equipment and CT examinations on dual-energy equipment using GSI.

Along with the study on the contribution of DWI in the diagnosis and monitoring of the evolution of renal malformations, new research directions are being opened that could validate or complete this type of investigation, namely:

- deepening the diffusion studies by using the other types of DWI sequences;

- indirect assessment of the degree of reversibility of fibrosis or subclinical fibrosis;

- study of the applicability of MRI elastography in the characterization of malformative diffuse renal diseases;

- identification of imaging correlations between renal DWI and renal MRI/US elastography.

The pilot study on the role of the SMART1 sequence (T1 mapping sequence) in the quantification of renal fibrosis should be continued in the following directions:

- enrollment of a much larger number of patients in order to expand the database and breakdown patients into lesion categories (malformative vs. non-malformative lesions, unilateral vs. bilateral lesions, focal lesions vs. diffuse lesions, separate study groups for each CKD category);

- extension of mapping techniques by introducing the T2 mapping sequence in the quantification of renal fibrosis;

- establishing correlations between T1 mapping-T2 mapping-DWI-ASL-BOLD sequences.

The multidirectional study of renal agenesis would require further completion in the following directions:

- comparing the compensatory increase of CSK with the compensatory increase of the single surgical kidney (post-nephrectomy of malformative cause, possibly also post-nephrectomy of another cause - tumor, inflammation) and establishing the predictive role of renal volume in the evolution to CKD; it should be noted that, to date, the number of patients with nephrectomy of malformative cause has been too small to allow a comparative analysis;

- establishing the functional impact of each of the CSK-associated malformations using comparative studies on each pathological entity (for example comparative studies between VUR associated with RA and pyelo-ureteral junction obstruction associated with RA, having as common comparison parameter GFR);

- the long-term correlation of the diagnostic accuracy of the malformations with surgical potential with studies of pathological anatomy on the operative parts.

In the future, artificial intelligence (AI) with applicability to the urinary tract will play an increasingly important role in the management of CAKUT. Imaging monitoring of hydronephrosis, atrophic kidney or cystic degeneration in ADPKD are just a few areas in which AI will contribute significantly as a functional prognostic factor for reno-urinary malformations.

Own contributions

- performing a comprehensive and detailed diagnostic analysis covering the entire CAKUT spectrum;

- making reliable radio-diagnostic correlations for the study of frequent lesional associations in renal and urinary malformation – chapter 6;

- realization and reliability of the SBCT protocol applied to children with CAKUT - chapter 7;

- comparative analysis of the ratio of radiation dose - diagnostic efficiency in children with CAKUT with emphasis on reducing radiation doses as a final goal - chapter 7;

- analysis and demonstration of the statistical relevance of the DWI sequence as a component of functional MRI in the diagnosis of fibrosis associated with chronic kidney disease - chapter 8;

- optimization of the SMART1 sequence as a T1 mapping sequence with applicability on the renal parenchyma - chapter 9;

- studying the reliability of the T1 mapping sequence in the diagnosis and monitoring of chronic kidney disease due to malformations - chapter 9;

- analysis of the degree of compensatory hypertrophy of CSK as a prognostic factor for the evolution towards CKD - chapter 10;

- analysis of the impact of malformations associated with renal agenesis on renal functional prognosis - chapter 10;

- analysis of the impact of malformations associated with renal agenesis on renal functional prognosis - chapter 10;

- creation of algorithms, radio-imaging diagnostic protocols, differential diagnostic tables and the stratification of the risk of progression to CKD, all acting as a diagnostic and monitoring guide applicable to all renal-urinary tract malformations - chapters 6, 7, 10.

Conclusions

The following conclusions can be drawn from this thesis:

1. Although anatomically very diverse, urinary malformations have highly variable functional impact, the more severe, the more malformative components are associated;

2. Diagnostic algorithms are essential in the complete diagnosis and detection of all renal and urinary malformations;

3. Ultrasound remains the screening and monitoring method of CAKUT;

4. Optimized SBCT protocols performed in addition to ultrasound provide complete diagnostic information with significant reduction in radiation dose, being ideal for pediatric examinations;

5. Functional MRI techniques such as DWI can provide valuable information on the status of the renal parenchyma and the potential for progression of renal dysfunction correlating with GFR and CKD stage;

6. T1 - weighted mapping sequences may have, in conjunction with other functional sequences, a significant contribution to global characterization of the renal parenchyma in terms of fibrotic changes occurring in the evolution of some renal malformations but require protocol adjustments to increase the accuracy of the method;

7. Compensatory hypertrophy is constituted as a reliable element for quantifying renal functional potential, renal volume correlating with GFR;

8. Early diagnosis (pre - and perinatal) and careful ultrasound monitoring is the key to choosing the optimal timing of surgery (if necessary) and detecting possible complications in time;

9. Complex malformative associations involving in particular the excretory tract and genital anomalies associated with RA have MRI (MRU, pelvic MRI) as an indication of choice.

Selective bibliography

(*out of the total of 211 references included in the thesis*)

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List of Published Scientific Paper

Scientific articles published in peer-reviewed journals

1. Is CT urography the best imaging method to evaluate renal tumors associated to horseshoe kidney? **Oana M. Rizea**, Cristina Al. Nicolae, Ioana G. Lupescu, Oncolog-Hematolog ro 50 (1)(1):p32-37, DOI:10.26416/OnHe.50.1.2020.2960.

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List of Papers Presented at Scientific Events

1. Assessement of imaging procedure in diagnose and follow up of obstructive urolithiasis in children, **Oana-Maria Rizea**, Bianca Șerban, Cristina Al. Nicolae, Ioana G. Lupescu, electronic poster, The Congress of the University of Medicine and Pharmacy Carol Davila Bucharest, Bucharest, June 02-04, 2016.

2. The contribution of radio-imaging methods in the diagnosis and monitoring of congenital ureteral dilatation in children, **Oana-Maria Rizea**, Cristina Al. Nicolae, Teodora Bărăscu, Ioana G. Lupescu, oral presentation, Conference "Fundeni Clinical Institute Days 2016", Poiana Brașov, September 29-October 2, 2016.

3. Radio-imaging aspects in renal and urinary congenital obstructive pathology, **Oana-Maria Rizea**, Cristina Al. Nicolae, Ioana G. Lupescu, oral presentation, 8th Europaediatrics

Congress jointly held with the 13 National Congress Romanian Paediatrics Society, Bucharest, România, June 07-10, 2017.

4. Radio-imaging aspects in renal and urinary congenital obstructive pathology, **Oana-Maria Rizea**, Cristina Al. Nicolae, Ioana G. Lupescu, oral presentation, SRIM Congress, October 05-08, 2017.

5. Imaging Diagnosis and Follow-Up of Dilatative Uropathies Associated with Unilateral Kidney Malformations: What Do We Choose And Why?, **Oana-Maria Rizea**, Cristina Al. Nicolae, Radu Nicolaescu, Ioana G. Lupescu, electronic poster, The Congress of the University of Medicine and Pharmacy Carol Davila Bucharest, June 07-09, 2018.

6. Radio-imaging in the Evaluation of Renal and Urinary System Malformations, oral presentation (course), **Oana-Maria Rizea**, Summer School in Radiology and Medical Imaging, Brasov, July 5-08, 2018.

7. The Essential of Radio-Imaging Methods In The Diagnosis And Follow-up Of Cystic Renal Lesions In Children, **Oana-Maria Rizea**, Cristina Al. Nicolae, Ioana G. Lupescu, electronic poster, The Congress of the University of Medicine and Pharmacy Carol Davila Bucharest, October 10-12, 2019.

8. Is Split-Bolus Technique Efficient in Reducing X-rays Exposure by CT Urography In Children?, **Oana M. Rizea**, Cristina Al. Nicolae, Ioana G. Lupescu, electronic poster, ECR (European Congress of Radiology) 2020.

9. T1 mapping in Pacients with Chronic Kidney Disease, **Oana M. Rizea**, Dana Tabac, Ioana G. Lupescu, Conference "Fundeni Clinical Institute Days", Bucharest, December 16-17, 2021.