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EVALUATION OF RENAL FUNCTION BY RADIONUCLIDE METHODS

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Summary. To point out the current role of nuclear medicine methods in nephrology and urology, biodistribution of commonly used radiopharmaceuticals, as well as techniques and clinical indications for their use are presented. Radionuclide methods assess both renal function and morphology. Considering mechanisms of renal handling of rediopharmaceuticals, the glomerular filtration rate is estimated by ^{99m}Tc–DTPA, while ^{131}I–hippuran is applied for measuring of the renal plasma flow and tubular function. Measurement of absolute clearances of these radiopharmaceuticals provides quantitative information concerning overall renal function, whereas dynamic renal scintigraphy yields relative individual kidney function. The functional information given by radionuclide methods, their noninvasive nature and the low radiation burden to the patient make them favorable for both diagnostic and monitoring tools of various renal diseases.

Key words: Radiopharmaceuticals, radionuclide methods, renal disease, nephrology, urology

The first attempt to asses the renal function with radionuclide applications was made in 1952 by Oeser and Billion, who measured urine radioactivity after intravenous injection of ^{131}I–iodoxyl (1). A further development of nuclear nephrology and urology was dependent on the construction of sensitive detectors and introduction of radionuclides with suitable physical and biological properties. In the past, a large number of compounds was applied to estimate kidney function and morphology, but only a few of them remained in clinical use. Currently, the most frequently used radiopharmaceuticals for this purpose are ^{131}I–orthoiodohippurate (^{131}I–OIH), ^{99m}Tc–diethylene–triamine–pentaacetic acid (^{99m}Tc–DTPA) and ^{99m}Tc–dimercaptosuccinic acid (^{99m}Tc–DMSA). Approximate values of factors influencing their biodistribution, as well as renal affinity and excretion mechanisms are shown in table 1.

Table 1. Biodistribution of renal radiopharmaceuticals

Radiopharmaceutical	Fraction bound to plasma proteins	Renal extraction coefficient	Renal pathway	Renal transit (min)	Renal cortical retention	Urinary elimination
131I–OIH	65%	80%	tubular secretion 80% glomerular filtration 20%	2.2	<5%	30 min–70%
^{99m}Tc–DTPA	<5%	30%	glomerular filtration	3.0	<5%	30 min–35%
^{99m}Tc–DMSA	90%	10%	tubular fixation	–	50%	2 hrs–10%

Orthoiodohippurate was labeled with ^{131}I and recommended for clinical estimation of the renal function in 1960 (2,3). After an intravenous injection about two thirds of the radiopharma–ceutical are reversibly bound to plasma proteins. Due to its very high renal extraction rate (4), ^{131}I–OIH is used as a major agent for the measurement of effective renal plasma flow (ERPF). About 80% of the extracted amount are cleared by active tubular secretion, while the rest is subjected to glomerular filtration (5). Rapid renal transit of ^{131}I–OIH enables its use for dynamic studies (6).

^{99m}Tc–diethylene–triamine–pentaacetic acid was introduced as a renal imaging agent in 1970 by

Hauser et al. (7). Many of its characteristics are close to those required for an ideal agent to quantify the glomerular filtration rate (GFR). Since only a small fraction is protein bound, DTPA penetrates the capillary wall and enters the extracelullar fluid. After an equilibrium of exchange between the vascular and extravascular space is established, plasma clearance of ^{99m}Tc–DTPA reflects GFR, since it is almost exclusively eliminated by that way (8). The renal transit is rapid and without a significant retention in the renal cortex (9). Biokinetics of DTPA associated with the possibility to be labeled by ^{99m}Tc, nearly ideal radionuclide, makes this radiopharmaceutical convenient for dynamic kidney imaging.

Lin et al.reported in 1974 a high rate of cortical retention of ^{99m}Tc–dimercaptosuccinic acid and proposed this radiopharmaceutical as an excellent agent for imaging of renal parenchyma (10). The disappereance rate of DMSA from the circulation is very slow, because it is tightly and almost completely bound to plasma proteins. Autoradiographic studies show that DMSA is fixed inside tubular epithelial cells (11). High cortical accumulation, associated with negligible urine elimination, enables sharp delineation of the renal cortex without interference of the collecting system. Such a distribution determines the primary use of DMSA as an imaging agent to assess morphological abnormalities. However, DMSA uptake was shown as a suitable index of both global and differential function of renal tubules, since the comparison studies confirmed a good agreement between DMSA uptake and ERPF values determined by ^{131}I–OIH (12).

Clearance determination and dynamic kidney scintigraphy are commonly used radionuclide techniques to evaluate the renal function (table 2). Clearance values should be considered as quantitative parameters of the renal plasma flow and glomerular filtration rate. The paraaminohippuric acid (PAHA) is accepted as a reference compound for ERPF evaluation, while inulin is used as a standard to estimate GFR. However, the procedures for determining PAHA and inulin clearances are very complex, requiring continuous intravenous injection of the agents, multiple blood samples to be drawn and bladder catheterization to collect urine.

The introduction of radiopharmaceuticals for clearance determination has shortened the analysis time and permitted easier and more accurate measurement by simplified procedures (table 3). Considering their kidney handling, ^{131}I–OIH is involved in ERPF measurement and ^{99m}Tc–DTPA to evaluate GFR. Clearance values obtained with these radiopharmaceuticals are slightly lower than those of reference compounds, but enough valuable for clinical use. Sapirstein's compartment analysis model (13) for creatinine clearance estimation was accepted as a basic principle for radionuclide techniques (14). This method requires only a single injection of the radiopharmaceutical followed by plasma sampling. Plasma samples are counted to assess the radioactivity disappearance rate, as a representative of plasma clearance, reflecting the renal function. The basic method of evaluating the complete disappearance curve using multiple blood samples is replaced today by the compartment analysis method, in order to reduce the number of blood samples. The two–compartmental model involves taking of 4–6 blood samples (15), while, if the one–compartmental model is used, only two blood samples are needed (16). Finally, the single sample technique was proposed on the basis of correlation observed

Table 2. Radionuclide methods for estimation of renal function

Radionuclide method	Radiopharmaceutical	Renal function	Type of information
Clearance	^{131}I–OIH	ERPF	quantitative
determination	^{99m}Tc–DTPA	GFR	qusntitative
Dynamic	^{131}I–OIH	ERPF	semiquantitative
scintigraphy		renal transit	quantitative
	^{99m}Tc–DTPA	renal perfusion	semiquantitative
		GFR	semiquantitative
		renal transit	quantitative
		urine flow	semiquantitative
Static scintigraphy	^{99m}Tc–DMSA	tubular function	semiquantitative

Table 3. Methods of clearance determination

Sample for measuring radioactivity	Number of blood samples	Postinjection time of sampling or counting	
		^{131}I–OIH	^{99m}Tc–DTPA
blood	6	Up to 60 min	up to 240 min
blood	2	20 and 30 min	120 and 180 min
blood	1	44 min	180 min
kidney	–	2–3 min	2 – 3 min

between the distribution volume of radiopharmaceutical and clearance values obtained with a standard method (17). Another simplification accepted is clearance measurement using only external counting of the kidney by the gamma camera (18). The method is designed by using comparison of the kidney uptake and known clearance values.

Dynamic kidney scintigraphy is performed by the computerized gamma camera, used to record radiopharmaceutical transit through the kidney. Radiopharmaceuticals with rapid renal transit, most commonly ^{99m}Tc–DTPA and ^{131}I–OIH, are used for this method. Serial images obtained for 20 minutes and renograms derived from the defined area of the kidney provide crude morphological and important functional information. Radiopharmaceutical kinetics through the kidney traces sequentially renal perfusion, parenchymal function and urine flow pattern.

Radiopharmaceutical arrival into renal vascularization can be observed visually through one second images obtained for the first 60 seconds. Such a rapid scintigraphy is possible to be made only with agents labeled by ^{99m}Tc. The ratio between the iliac artery and renal activity during the first pass of the radiopharmaceutical represents a perfusion index for semiquantitative estimation of renal perfusion (19).

The data acquired at 20 second intervals within 1–3 minutes period of scintigraphy reflect parenchymal function. Computer analysis of the time activity curve is used to calculate semiquantitative parameters of the renal function, such as the relative uptake of radiopharmaceutical, slope of the ascending segment, time of the curve maximal activity and excretory index. By comparing the slope or uptake value of one kidney to that of the other kidney individual renal function can be determined (20). By multiplying the relative values expressed as a percentage of distribution of global function between the two kidneys with the global clearance value,the absolute measure of separate renal clearances is obtained. To exclude extrarenal factors from interfering, deconvolution analysis is introduced to yield retention function and renal transit times, as quantitative parameters of nearly physiological components of renal function (6,9).

A scintigraphic estimation of renal excretion function is made by visualizing radiopharmaceutical clearing from the collecting system or calculating radioactivity retention. The delineation of the pelvicalyceal system is well obtained by 99mTc–DTPA images.

Since ^{131}I has no appropriate physical characteristics for gamma camera scintigraphy, the quality of ^{131}I–OIH image is poor. Therefore, there is a search for a suitable agent to be labeled with ^{99m}Tc and secreted by tubules. Up to now the best results have been achieved with ^{99m}Tc–MAG3 (21). However, although better images are obtained with this new radiopharmaceutical, ^{131}I–OIH remains an agent of choice for scintigraphy in patients with renal failure due to its higher renal extraction ratio.

Several modified methods of dynamic scintigraphy are helpful in particular kidney disorders. Stimulation of diuresis by furosemide injection is aimed to differentiate obstructive from non–obstructive diseases (22). Captopril induced inhibition of angiotensin convertyng enzyme leads to a decrease of GFR and tubular function in the kidney with stenotic renal artery (23). Indirect radionuclide cystography is used to detect vesico–ureteral reflux, as a reappearance of ureteral and kidney activity after its elimination (24).

Radionuclide methods have an important role for the evaluation of renal function, involved for diagnosis, prognostic purposes and follow–up of kidney patients (table 4).

Vascular disorders. Diminished renal perfusion is a primary disturbance in patients with renal artery stenosis, while depression of ERPF and delay in parenchymal transit time occurs consequently. The captopril test was shown to have a high sensitivity in the detection of renal vascular hypertension. Inhibition of angiotensin converting enzyme is followed by a considerable decrease of glomerular filtration due to the dilation of the efferent arterioles. Renal infarction is often missed by other visualization techniques, but revealed reliably by radionuclide techniques, as a peripheral area lacking perfusion and uptake. In patients with renal venous thrombosis various degrees of perfusion and function impairment can be observed.

Parenchymal diseases. Urographic finding is often normal in patients with a relatively mild impairment of the renal function, while radionuclide methods are very sensitive, even in the initial stage of disease. Renal hypofunction is manifested by low radiopharmaceutical uptake, prolonged transit time and decreased clearance value. By using radiopharmaceuticals with different mechanisms of renal handling, it is possible to estimate the extent of renal dysfunction, as well as to monitor the changes characteristic for disease in the advanced stage.

The results of our previous study of patients with endemic nephropathy and glomerulonephritis are shown in table 5 (25). Dynamic kidney scintigraphy and determination of ^{99m}Tc–DTPA and ^{131}I–OIH clearance in endemic nephropathy patients indicated a bilateral impairment of both

Table 4. Nephrologic indications for radionucliide methods

Renal disease	Radionuclide methods	The aim of examination
1. Renal artery stenosis	Dynamic scintigraphy	Diagnosis
	Captopril test	Prognosis
	Perfusion scintigraphy	Evaluation of treatment
	Clearance determination	
2. Renal infarction	Perfusion scintigraphy	Diagnosis
	Dynamic scintigraphy	
	Clearance determination	
	Static scintigraphy	
3. Diffuse parenchymal disease	Dynamic scintigraphy	Diagnosis
	Clearance determination	Follow up
		Evaluation of treatment
4. Obstructive disease	Dynamic scintigraphy	Diagnosis
	Diuretic scintigraphy	Prognosis
	Clearance determination	Follow up
		Choice of treatment
		Evaluation of treatment
5. Acute renal failure	Dynamic scintigraphy	Diagnosis
	Clearance determination	Prognosis
		Follow up
		Evaluation of treatment
6. Chronic renal failure	Dynamic scintigraphy	Follow up
	Clearance determination	Choice of treatment
7. Renal transplantation	Dynamic scintigraphy	Selection of graft donors
	Clearance determination	Follow up
	Perfusion scintigraphy	Diagnosis of complication
8. Space occupying lesions	Static scintigraphy	Differential diagnosis
	Perfusion scintigraphy	Follow up
	Dynamic scintigraphy	
9. Traumatic lesions	Dynamic scintigraphy	Diagnosis
	Perfusion scintigraphy	Follow up
10. Vesicoureteral reflux	Radionuclide cystography	Diagnosis
	Clearance determination	Prognosis
		Follow up
		Evaluation of treatment

Table 5. ^{99m}Tc–DTPA and ^{131}I–OIH clearance values in patients with endemic nephropathy and glomerulonephritis

Group	Number of patients	^{99m}Tc–DTPA clearance (ml/s)	Number of patients	^{131}I–OIH clearance (ml/s)
1. Control	31	2.04 ± 0.28	30	9.11 ± 1.66
2. EN	26	1.09 ± 0.52^{A}	26	4.14 ± 1.16^{A}
3. EN–CRF	24	0.29 ± 16A^{C}	24	1.83 ± 0.53^{AC}
4. GN	19	1.75 ± 0.53^{B}	14	7.52 ± 2.49^{B}
5. GN–CRF	10	0.77 ± 0.47^{AD}	9	4.31 ± 2.04^{AE}

Statistical significance vs.control: A p<0.001, B p<0.01; EN vs. EN–CRF: C p<0.01; GN vs GN–CRF: D p<0.01, E p <0.01
EN = endemic nephropathy
GN = glomerulonephritis
CRF = chronic renal failure

the glomerular and tubular function, but this latter was more frequently reduced in the early stage of disease. Dependent on the type and stage of disease GFR in some patients with glomerulonephritis was found unchanged, but depressed in others. ^{131}I–OIH clearance values of individual patients were occasionally decreased, while the mean clearance values of both radiopharmaceuticals were slightly lowered. When endemic nephropathy and glomerulonephritis were associated with chronic renal failure a very considerable functional impairment was observed. Similar finding of ^{99m}Tc–DTPA and ^{131}I–OIH application was obtained in our other studies on patients with parenchymal diseases (26,27,28).

Determination of ^{99m}Tc–DMSA renal fixation showed markedly decreased uptake in endemic nephropathy patients, while somewhat decreased but without a statistical significance in glomerulonephritis patients (29,30). This finding associated with ^{99m}Tc–DTPA clearance values simultaneously measured point at the impairment of both tubular and glomerular functions in endemic nephropathy, while in glomerulonephritis the impairment of glomerular filtration was more pronounced (29,30).

In patients with pyelonephritis a considerable disturbance in urine drainage may be observed as the first sign, followed later by a decrease of renal plasma flow. ^{99m}Tc–DTPA dynamic scintigraphic study of the patient with chronic atrophic pyelonephritis of the left kidney is presented in fig. 1. A very small sized kidney with poor function can be seen.

Diabetic patients with incipient renal changes may have microalbuminuria but unchanged GFR and ERPF, but when diabetic nephropathy is fully developed a reduction of both functional parameters is unequivocally observed (31).

Obstructive disease. Characteristic scintigraphic finding of impaired urine outflow due to obstruction is radiopharmaceutical accumulation in a dilated renal pelvis, combined with an ascending type of renogram. However, non–obstructed flaccid, voluminous pelvicalyceal system is presented scintigraphically by the same finding. To differentiate the two disorders diuretic scintigraphy has to be used. A furosemide injection fails to promote elimination of activity from the collecting system of patients with obstructive disease, while a rapid response is obtained in non–obstructive disorder (22).

The use of dynamic scintigraphy in patients with obstructive disease is of primary significance to estimate renal function, since long term retrograde pressure of the urine causes an irreversible kidney damage. ^{99m}Tc–DTPA dynamic scintigraphy of the patients with a hydronephrotic left kidney due to chronic obstruction by stone is shown in fig. 2. From serial kidney images and the

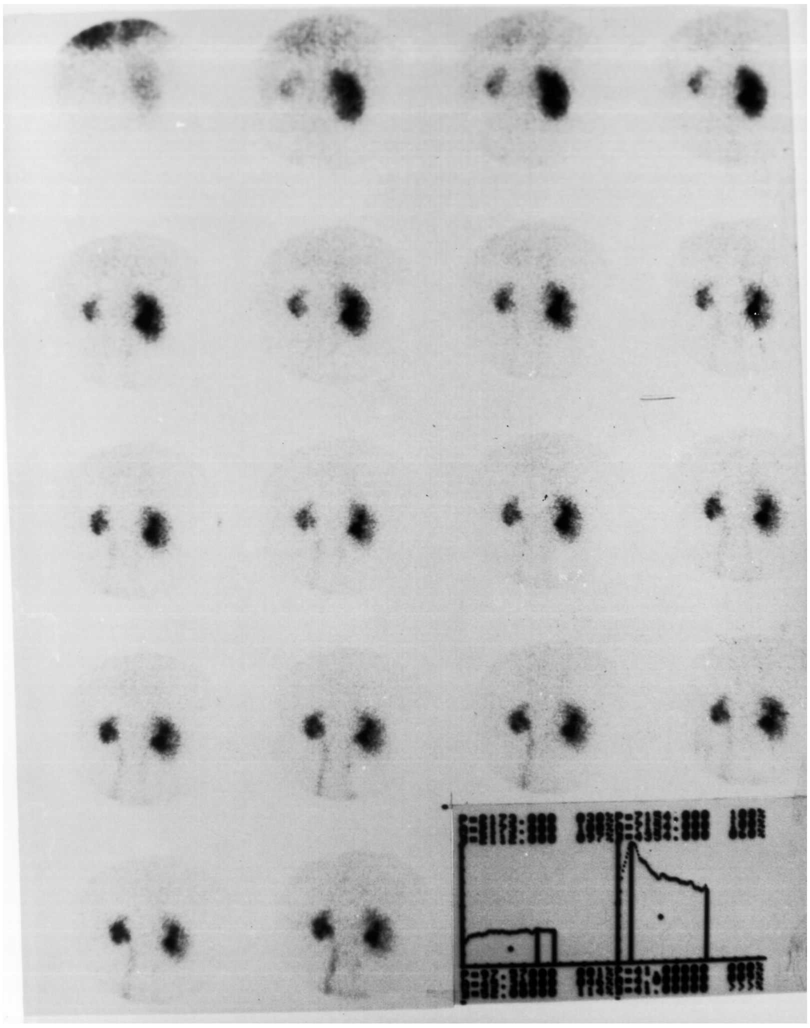

Fig. 1. ^{99m}Tc–DTPA dynamic scintigraphy of a patients with chronic pyelonephritis of the left kidney.

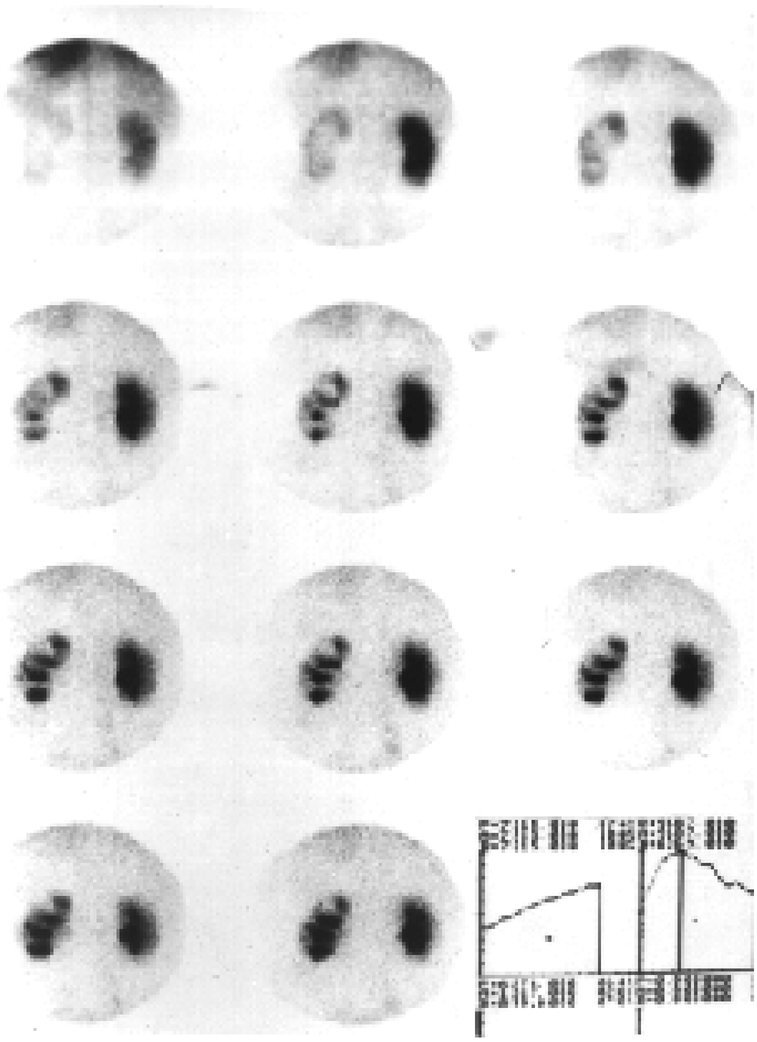

Fig. 2. ^{99m} Tc–DTPA dynamic scintigraphy of a patient with hydronephrosis of the left kidney.

time activity curve, poor residual parenchyma and enlarged collecting system, with low uptake and absent elimination of the radiopharmaceutical can be seen. On the basis of the estimated renal function the probability of functional recovery after surgical treatment may be predicted (34). The prediction is particularly helpful in the non–visualizing kidney by urography, since good residual renal circulation and glomerular filtration, shown by radionuclide method, promise a chance of the restoration of kidney function after relieving obstruction (35,36). Postsurgical follow up evaluates the efficacy of the treatment.

Renal failure. An abrupt and huge decrease in GFR is the most striking finding in oligoanuric phase of acute renal failure (37,38). Repeated radionuclide examinations of these patients have to be performed in order to recognize the trend of renal function recovery or the occurrence of irreversible kidney damage (39,40). Since the renal plasma flow is better preserved than glomerular filtration, ^{131}I–OIH uptake is accepted as a prognostic parameter.

The determination of chronic renal failure obtained by radionuclide methods is generally independent on the underlying kidney disease, being similar for most etiologies. Small kidneys with poor and delayed uptake leading to prolonged excretion is usually present (40). The clearance value of both ^{99m}Tc–DTPA and ^{131}I–OIH is very small.Since ^{131}I– OIH concentrates even in the kidney with minimal residual function, the absence of its uptake is associated with an extremely poor prognosis.

Renal transplantation. Radionuclide methods are used in various phases of transplantation, including graft donor selection, monitoring of transplanted kidney function and detection of possible complications. Scintigraphic examinations are done serially from the very day of surgical treatment. The patency of blood vessel and ureteral anastomosis can be easily established by dynamic scintigraphy. Surgical complications of vascular (41) or urologic (42) origin do not differ scintigraphically from those of the native kidney. Radionuclide method use is especially important in detection of acute renal failure, since a positive finding usually precedes biochemical abnormalities. Acute renal failure is mostly caused by acute rejection, or acute tubular necrosis of the graft. Common changes in both disorders are prolongation of the cortical transit time and impaired excretion function. However, these changes are quickly followed by a decline in the renal blood flow in the initial stage of acute tubular necrosis (19). In advanced stage, acute tubular necrosis is also associated with a reduction of renal perfusion (43). The particular mode of scintigraphy, using 99mTc–colloid, ^{131}I–fibrinogen or ^{111}In–leukocytes can be also involved in differentiating these complications. Radionuclide studies of the graft function in the late post–transplant period have also to be performed due to a possible occurrence of chronic rejection, as a slow process characterized by a gradual deterioration of graft function (44).

Other renal diseases. In some cases of horseshoe and ectopic kidney hemodynamic and urine flow disturbances can be proven by the radionuclide method, since blood vessels and ureters may be twisted or compressed by altered kidney position and morphology (45).

The earliest abnormality found in polycystic kidneys is delayed excretion by the cortical tissue, manifested as a prolonged transit time. Progressive reduction of renal parenchyma due to cysts enlargement is accompanied by GFR and ERPF impairment.

Space occupying lesions are scintigraphically presented by a non specific finding of focal afunctional areas, but perfusion studies may be useful to differentiate vascularized from non–vascularized pathologic alterations. Extended lesions can affect total renal function due to the reduction of renal parenchyma, compression of blood vessels or impairment of the urine outflow. In our study of 21 patients with an upper urinary tract urothelial tumor, ^{99m}Tc–DTPA clearance value and perfusion were found reduced in the kidney on the tumor side (46). The differences observed in the degree of impairment could be attributed to the type of cancer, location and evolution stage.

A radionuclide examination of traumatic lesions of the kidney presents a variety of blood vessels, renal parenchyma and collecting system damages.

Children with a urinary tract infection, as a group with high incidence of vesicoureteral reflux, have to be subjected to radionuclide cystography. Besides reflux detection, the function of the kidney on the reflux side can be evaluated by indirect radionuclide cystography, during the same procedure with a single dose.

Radionuclide methods provide information of both the renal function and morphology. With few exceptions nuclear morphologic methods are not first line procedure in nephrology, since other visualization techniques offer greater sensitivity. However, information about the renal function obtained by radionuclide methods is often not available by other methods. Using radiopharmaceutical with different renal handling, the glomerular filtration rate and renal plasma flow can be estimated separately. By clearance determination the global function of both kidneys is assessed quantitatively, but when combined with dynamic scintigraphy separate clearance values of each kidney can be calculated. Apart from the parenchymal function, renal perfusion and urine flow can be evaluated separately by dynamic kidney imaging. Due to use of tracer amounts, radiopharmaceutical applications do not disturb physiological processes and no side effects are reported. The simplicity of the procedure, non invasive nature and low absorbed radiation doses make radionuclide studies as methods of choice for diagnosis, prognosis and follow– up of patients with kidney diseases.

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PROCENA BUBREŽNE FUNKCIJE RADIONUKLIDNIM METODAMA

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Sažetak. Sa ciljem da se istakne značaj radionuklidnih metoda u nefrologiji i urologiji dat je pregled osnovnih principa njihovog izvodjenja, informacija koje pružaju i indikacija za primenu. Korišćenje radiofarmaka se zasniva na njihovom afinitetu za vezivanje u bubregu, ili specifičnom mehanizmu izlučivanja iz bubrega. Vezivanje ^{99m}Tc–DMSA u bubregu omogućuje morfološko ispitivanje metodom statičke scintigrafije. Radiofarmaci sa brzim izlučivanjem se koriste za procenu funkcije bubrega. ^{131}J–hipuran se pretežno eliminiše mehanizmom tubulske sekrecije i koristi se za ispitivanje ove funkcije, a zbog velike bubrežne ekstrakcije i za procenu renalnog protoka plazme. Skoro isključiva eliminacija ^{99m}Tc–DTPA putem glomerulske filtracije omogućuje merenje ove funkcije. Vrednosti klirensa ^{131}J–hipurana i ^{99m}Tc–DTPA predstavljaju kvantitativne parametre odgovarajućih funkcija bubrega. Dinamskom scintigrafijom bubrega dobijaju se kompjuterizovani radiorenogrami za semikvantitativnu procenu perfuzije, funkcije parenhima i ekskretorne funkcije bubrega, dok dekonvolucijska obrada podataka daje i kvantitativne funkcijske parametre. Pojedinačna funkcija bubrega se izračunava iz vrednosti preuzimanja radiofarmaka u bubregu. Kvantitativno odredjivanje funkcije svakog bubrega posebno, neinvazivnost i mala apsorbovana doza zračenja čine radionuklidne metode pogodnim za primenu u dijagnozi i praćenju toka mnogih bubrežnih bolesti.

Ključne reči: Radiofarmaci, radionuklidne metode, bubrežne bolesti, nefrologija, urologija

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