

УДК 616-073.96:616-039.76:616-06

DOI: <http://doi.org/10.31928/2305-3127-2023.3-4.5363>**M.V. Satyr, I.V. Noverko, T.I. Pantus, M.S. Zagriichuk**

Heart Institute of the Ministry of Health of Ukraine, Kyiv, Ukraine

Significance of nuclear medicine methods for diagnosis and predicting the course of renal transplantation complications

Renal transplantation is a replacement-based therapeutic method in end-stage kidney failure. It is based on the interdisciplinary collaboration between scientists and clinicians, which match together the achievements of surgery, immunology, and radiation diagnostics. After transplantation the complications appear, which can be associated with status of the graft, the immunological factors of compatibility between the donor and the recipient, the surgical intervention. Early diagnosis and forehanded treatment of such complications is important, as it helps to evaluate and predict the functionality of the graft.

In this article we discuss the complications after kidney transplantation: the reasons of their occurrence, pathogenesis, clinical features, and radiation imaging signs. The opportunities of the radiology methods for the differential diagnostics of complications which appear before, during or after the surgery, are shown.

We pay the main attention to the nuclear medicine methods, especially the dynamic renal scintigraphy (DRSG) as a method for the evaluation of graft functionality. This is a safe, accessible and non-invasive method for evaluation the quantitative and qualitative parameters of kidney function. DRSG consequently characterizes the perfusion, the extraction and the excretion in the studied organ. We display the standard DRSG protocols using [^{99m}Tc] Tc-MAG3 and [^{99m}Tc] Tc-DTPA radiopharmaceuticals. We analyze investigations of kinetic perfusion and parenchymal DRSG parameters and their importance for differential diagnosis of complications, prognosis on delayed and slow graft function, short-term and long-term graft functionality assessment. We make an accent on the prognostic importance of the dynamic changes visible on DRSG.

We discuss the perspectives of further development of scintigraphic methods for the assessment of kidney grafts. It is related to the implementation of high-quality 3-dimensional visualization, newest radiopharmaceuticals. We conclude the importance of the nuclear medicine as an element of multidisciplinary approach in transplantology.

Key words: complications of kidney transplantation, dynamic renal scintigraphy, kinetic perfusion and parenchymal functional parameters

History of the development of renal transplantation and diagnostic visualization. Current state of transplantology in Ukraine

Renal transplantation is a special substitution treatment for end-stage renal failure, involving the transplantation of an organ from a living or deceased donor to the recipient. It is the method of choice and the only method to save the life of hopeless patients [1, 2, 14].

Transplantology is an independent branch of health care that combines the achievements of many areas of medical science and practice. The availability of transplantation care determines the level of healthcare development in general [2, 14].

An active transplantation practice has been functioning for more than half a century worldwide and is based on interdisciplinary collaboration between physicians and scientists [9]. The historical development of transplantology and diagnostic imaging has

taken place in parallel. The acquisition of the first X-ray images by Conrad Röntgen (1895), the discovery of the phenomenon of radioactivity by Henri Becquerel (1896) and the work with gamma rays by Marie Skłodowska-Curie (1898–1903) coincided with the first attempts at kidney transplantation in animals by Emmerich Ullman and Alexis Carrel (1902). And in 1933, when our compatriot Yurii Voronyi performed the first transplant of kidney from human to human, artificial gamma emitters were discovered in France (by Irene Joliot-Curie, Marie and Pierre Curie) and the creation of basic substances for nuclear medicine – ^{131}I and $^{99\text{m}}\text{Tc}$ – began. Innovations in radiology and nuclear medicine were intensively developed in the 1950s and 1960s, at the same time the «golden era» in renal transplantation began [9].

In Ukraine, 2,115 patients need kidney transplantation every year. However, organ transplants account for only 0.8 % of all surgical interventions. According to the data of the Ministry of Health of Ukraine of 2016, only two cadaveric kidney transplantations and 93 family kidney transplantations have been performed in Ukraine. In 2017 there were 118 operations and in 2018 there were 96, before entry into force of the Law of Ukraine «On the Application of Transplantation of Anatomical Materials to Humans» came into force [1, 3]. According to the latest information of the Ukrainian Center for Transplant Coordination, 231 renal transplantations were performed in 2021 (126 from a living donor, 105 from a deceased donor), 274 – in 2022 (134 from a living donor, 140 from a deceased donor), and 176 – in January–June 2023.

Complications following renal transplantation

A renal transplantation is a complex medical procedure involving prior analysis of compatibility between donor and recipient, adequate preparation of the transplant, and perfect technical execution of the surgical procedure. Failure at any stage can lead to the reversible or irreversible complications. In order to prevent them, careful examination of the donor and recipient is carried out during the preparation for transplantation [1, 2, 13, 37].

When transplanting from a cadaver, it is important to minimize cold and heat ischaemia to reduce ischaemic damage to the kidneys [2, 37]. Living donors are subjected to anatomical and functional renal assessment and immunological compatibility testing. By now, a five-year survival rate of a transplanted kidney has increased from 72 to 99 % [30]. The prognosis for the success of the procedure and graft survival is better than that of living donors

(1-year survival of a graft from a living related donor is 90–95 %, from a cadaveric donor – 80–90 % [14, 37].

Complications can occur due to the condition of the graft, the immunological relationship between the recipient and the graft, and the consequences of surgical intervention. In general, they can be divided into 3 large groups – pre-surgical (graft-related), non-surgical (mainly autoimmune) and surgical-related (vascular and non-vascular) (Table 1) [8, 13, 14, 23, 29, 31, 37]. All complications have different factors and a usual time of occurrence.

Methods of the diagnosis of transplantation complications. Place of nuclear medicine methods

Clinical manifestations of various complications are manifested by fever, pain in the graft area and its enlargement. A differential diagnosis of the different conditions may be complicated by their coincidence in time (for example, ATN and HAR) [1, 2]. Establishing the aetiology, the level of perfusion and graft functioning are extremely important for the early diagnosis of the complication, since the correct choice of correction and the subsequent prognosis depend on it. Doppler ultrasound is a method of choice for assessing complications in the early post-operative period and long-term follow-up [13, 14, 15, 30, 37]. This study is able to detect parenchymal changes, blood flow abnormalities. The possibilities of the method are limited in the diagnosis of ATN, rejection or toxicity of immunosuppressants [29, 37]. The graft dysfunction might be predicated by the changes of an indirect indicator of post-stenotic renal flow – the resistance index (IR). However, it is non-specific and does not allow to differentiate complications [34].

X-ray techniques (excretory urography, CT with angiography) clearly define the morphological characteristics of the graft and surrounding tissues and reveal structural changes in the renal vessels, parenchyma and calyx-pelvis complex, the consequences of obstruction and oedema [4, 30, 37]. However, these methods are ineffective in functional changes, and the use of iodine-containing contrast media is not recommended because of their high nephrotoxicity [14, 30, 37].

Biopsy is a gold standard for assessing morphological changes in graft tissues and identifying the causes of graft dysfunction [11, 14, 37]. However, it is an invasive technique that can cause complications. It is contraindicated in uncontrolled hypertension, active kidney or perineal infection, hydro-nephrosis, $\text{IR} \geq 1.5$ [29]. In recent decades, the use of biopsy has decreased [13].

Table 1

Classification of the most common complications of renal transplantation and the time of their occurrence

Complication	Time of occurrence postoperatively	Comments
Pre-surgical		
ATN	Minutes, hours	Occurs during cadaveric transplantation; function may be restored within days-weeks
Non-surgical		
HAR	Minutes, hours	Caused by antibodies, irreversible
AAR	1–5 days	History of hemotransfusion, transplantation in the anamnesis
AR	More than 5 days, more often – the first 3 months	Cell-mediated, responsive to treatment
CAN	Months, years	Humoral, irreversible
Immunosuppressant nephrotoxicity	Months	Dose-dependent, reversible upon drug withdrawal
Surgical-related		
<i>A) Vascular</i>		
Renal graft artery stenosis	More than 1 month	
Renal graft vein stenosis	More than 1 month	
Renal graft artery thrombosis	Days, weeks	Irreversible
Renal graft vein thrombosis	First week	Caused by the lack of draining collaterals
<i>B) Non-vascular</i>		
Urine leak (urinoma)	Days, weeks	
Hematoma	The first few days	
Infection (abscess)	The first few days	
Lymphocele	2–4 months	Caused by destroying of lymphatic ducts
Urinary tract obstruction, VUR	Days, months, years	

ATN – acute tubular necrosis (vasomotor nephropathy); HAR – hyperacute rejection; AAR – accelerated acute rejection; AR – acute rejection; CAN – chronic allograft nephropathy (chronic rejection); VUR – vesicoureteral reflux.

Radionuclide studies provide unique information in the study of disorders of perfusion, parenchymal and excretory function of the kidneys. They cause minimal radiation exposure to the patient and do not require special preparation or sedation [13, 29].

Dynamic renoscintigraphy (DRSG) is a safe, widely available, non-invasive method of assessing quantitative and qualitative parameters of renal graft functioning. The study sequentially characterises the main phases: angiographic – assessment of perfusion during the first pass after bolus administration of a radiopharmaceutical (RPH); dynamic – determination of glomerular filtration rate (GFR) and effective renal plasma flow (ERPF); excretory (characterisation of the calyx-pelvis complex) [6, 13]. DRSG can distinguish the functional contribution of the graft from the residual function of the kidneys themselves or

of previously failed transplants, localize areas of non-functioning parenchyma, and identify surgical complications [16].

Against the background of intensive development of new functional imaging technologies (ultrasound Doppler, MRI, X-ray CT), the approaches of specialists of different specialties to the application of DRSG in renal transplant examination have changed [13].

In the practice guidelines of the European Association of Nuclear Medicine (2018), the status of a transplanted kidney is a clinical indication for DRSG [16].

The American College of Radiology (ACR) in consensus with European Society of Radiology (ESR) indicates DRSG with [^{99m}Tc] Tc-MAG3 as a procedure that has a complementary value for the quantitative assessment of three consecu-

tive phases of renal graft function. DRSG with tubular radiopharmaceutical has 7 points on the application rating scale, which corresponds to the «usually appropriate» level, and DRSG with glomerular radiopharmaceutical – 5 points, which corresponds to the «may be appropriate» level [30].

In the practical recommendations of the European Association of Urologists, after the widespread introduction of ultrasound with colour Doppler mapping into the world practice, the routine use of DRSG to assess the functioning of the transplant is not recommended [14]. But in the paediatric population, DRSG with [^{99m}Tc] Tc-MAG3 is recommended for evaluation of excretory function or when the urological complication (urine leakage) is suspected [18].

In many medical centres, DRSG is routinely performed in the early post-transplant period to provide a baseline information for further comparative evaluation in case of complications. Laboratory (creatinine level) or X-ray examination do not provide information on the functional state of the graft [23, 30, 37].

Radiopharmaceuticals used to determine the graft function. Scintigraphic study protocol

One of the main functions of the kidneys is to remove waste products from the body by filtering the blood. The structural and functional unit of the kidney is the nephron, consisting of a system of glomeruli and tubules. Glomerular filtration of blood occurs passively under the influence of effective filtration pressure (depends on the oncotic pressure of blood plasma and the state of glomerular permeability). Tubular secretion of organic compounds and their secretion into the lumen of proximal tubules is an active transport against the concentration gradient [13, 16, 37].

Depending on the purpose of the study, DRSG is performed with different radiopharmaceutical agents.

To determine the GFR, radiopharmaceuticals with low chemical reactivity, freely penetrating the extracellular space and filtered in the glomeruli, not reabsorbed and not subject to secretion, are used [13, 37]. The most common RPH is [^{99m}Tc] Tc – DTPA (diethylenetriaminopentaacetic acid, with a molecular weight (393 g/mol), labelled [^{99m}Tc]): after administration, the drug quickly leaves the bloodstream by glomerular filtration, bind to plasma proteins by 10 %. It does not cross the blood-brain barrier, overcomes the alveolar-capillary membrane. It is not absorbed after injection. It does not accu-

multate in the kidneys, 90 % of the administered dose is excreted in the urine in the first 24 hours by glomerular filtration [6, 16].

The effective dose for [^{99m}Tc] Tc-DTPA ranges from: 0.18–0.91 mSv/per study (depending on kidney function) [6, 16].

To determine the ERPF, which characterizes the tubular secretion, RPH of tubular elimination are used – [^{99m}Tc] Tc-MAG3 (mercaptoacetyltriglycine) with a molecular weight of 263 g/mol. After intravenous administration, 50 % of the drug is secreted in the proximal parts of the tubules by transporters of organic anions, after which it is strongly but reversibly bound to plasma proteins by 80–90 %. The extraction rate during the first passage through the tubular system is 55 %. After 2 hours, 90 % of RPH is excreted in the bladder, 10 % is eliminated by the hepatobiliary system.

The effective dose for [^{99m}Tc] Tc-MAG3 is: 0.53 mSv/per study [6, 16].

Study protocol [13, 16, 37]:

When performing DRSG, the supine position is preferred; detector is placed over the graft area (in the iliac region). It is recommended that part of the recipient's kidneys be brought into view, as they may be partially functional, as well as at least part of the bladder.

Preparation: an hour before the examination, adults are recommended to drink 300–500 ml of liquid within 30 minutes. Children can be hydrated intravenously (10–15 ml/kg). Empty the bladder before the examination.

Calculation of RPH activity for study:

1) [^{99m}Tc]Tc-MAG3:

Children: 0.1 mCi/kg (3.7 MBq/kg), minimum dose 1 mCi (37 MBq);

adults: 2.5–5 mCi (93–185 MBq).

2) [^{99m}Tc] Tc-DTPA:

Children: 0.05 mCi /kg (1.9 MBq/kg), minimum dose 1 mCi (37 MBq);

adults: 5–10 mCi (185–370 MBq).

Equipment: gamma camera with a large field of view; low-energy, high-resolution collimator; photo-peak 140 keV (window 15–20 %).

Patient position: lying on the back; the RPH is administered under the detector, rapidly, bolus-like. Collection of the flow phase begins at the moment of visualization of the aorta, collection of the parenchymal phase – immediately after the vascular phase.

Collection parameters: flow first-pass phase (radionuclide angiography) – 60 seconds (1–2 frames per minute); parenchymal (extractive-excretory) phase – 25–30 min 2 frames/min.

Processing: determine the vascular (aorta or iliac artery) and renal (graft, kidney) zones of inter-

Table 2

Perfusion and parenchymal kinetic parameters of DRSG**Perfusion parameters**

Hilson's index	The ratio of area under the arterial and renal curves from the time of injection to peak of the arterial curve
P	Peak perfusion time (sec)
ΔP	The difference in the time of peak perfusion of the transplant and the aorta (sec)
Kirchner's index	The ratio of the main ascending portions of the graft and aorta curves. The normal range is 0.64–1.16
P: PI	The ratio of the peak count to the plateau count
T1/2 washout	T1/2 of the descending part of the perfusion curve of the graft (sec)
Perfusion ratio of the graft and the aorta	Ratio of graft and aorta perfusion peak counts
Slope of the 2nd phase of the perfusion curve	30–60 sec
Graft index (GI)	Perfusion and graft function in the first 3 minutes: $GI = (\Delta P \times \text{arterial peak} \cdot \text{plateau}) / (\text{perfusion peak} \cdot \text{uptake at 3 minutes})$

Parenchymal functional parameters (extractive and excretory)

Peak perfusion/accumulation	Ratio of peak perfusion and accumulation accounts
Tmax	Time of peak (maximum) activity (min)
2 MU	MAG3 fixation at 2 minutes
T1/2	Half-life (min)
R20 (retention index)	Retention index (ratio of activity in the renal parenchyma at 20 min to peak activity)
R20/3 (accumulation index)	Accumulation index (ratio of counts for 20 and 3 minutes)

est, background zones, generate time-activity curves and calculate the differential function of the graft and kidneys [6, 37]. Perfusion and parenchymal kinetic parameters are calculated during the processing of the results (Table 2) [6, 31, 33].

The iliac artery is recommended as the vascular area of interest for calculation of perfusion parameters, as soft tissue signal attenuation is lower in this area compared with the aorta [21].

The protocol may vary according to the type of complication: with renal artery stenosis, a study protocol with angiotensin converting enzyme (ACE) inhibitors is used; with hydronephrosis or obstruction – a diuretic protocol [37].

Delayed imaging (1–2 hours) may clarify the causes of fluid accumulation and reveal probable urine leakage [37].

When interpreting the findings, the type of graft (from a cadaver, a native or a non-native donor), the time of investigation since transplantation (different complications have a certain time of occurrence), the clinical picture, the laboratory results and the current treatment should be taken into account [6, 37].

Characteristics of complications and possibilities of the diagnostic imaging for their differential diagnosis

PRE-SURGICAL AND NON-SURGICAL COMPLICATIONS:

Pre-surgical complications include ATN resulting from damage to the graft before the start of the transplantation.

Non-surgical complications are associated with immunological reactions (superacute, accelerated acute, acute and chronic rejection) or the toxic effect of immunosuppressants [1, 14].

The differential diagnosis of these conditions is very important for their correction and subsequent graft survival.

The gold standard for differential diagnosis of pre-surgical and non-surgical complications is ultrasound-guided biopsy [8, 15]. A disadvantage of the method is the likelihood of complications due to invasiveness and contraindications [8].

Ultrasound reveals non-specific signs of renal dysfunction: increased organ size, increased cortical density, decreased corticomedullary differentiation,

Table 3
Comparison of scintigraphic signs of ATN and AR

Complication	Perfusion parameters	Baseline DRSG parameters	Follow-up DRSG parameters	Renal transit parameters
ATN	Normal	Abnormal	Improves	Raised up
AR	Slowed down	Normal	Worsens	Raised up

ATN – acute tubular necrosis (vasomotor nephropathy); AR – acute rejection.

pyramidal contrast, thickening of the harvesting elements, and flattening of the central sinus echocomplex [29]. IR increases with graft dysfunction (IR > 0.8 – with rejection) [15].

The scintigraphic pattern of pre-surgical and non-surgical complications differs and can be used for their differential diagnosis.

Acute tubular necrosis (ATN) is one of the most common complications (about 15 % of cases) arising from cadaveric kidney transplantation and is the result of reperfusion injuries before implantation [15, 23]. ATN causes delayed graft function and the need for hemodialysis in the first days (weeks) after surgery.

Pathogenetically: ischaemic damage to the vascular endothelium and destructive changes to the graft tubules due to prolonged cold or heat ischaemia [37].

It is clinically manifested by reduced renal functional capacity. It usually resolves spontaneously within the first two weeks. If the process is prolonged, another pathology should be suspected [15, 37].

Scintigraphically: in the early postoperative period, perfusion parameters are within normal limits; parenchymal parameters are slowed down, increased cortical retention (increased T-max, T-1/2 and R20/3 times). On repeat examination, all parameters improved over time [15, 29, 37].

Hyperacute rejection (HAR) is due to a conflict in histocompatibility antigen or blood group. It occurs immediately after the creation of a vascular anastomosis, detected during surgery, is irreversible and requires immediate removal of the graft [37].

Accelerated acute rejection (AAR) results from antibody sensitisation of pregnancy or frequent haemotransfusions occurring on day 1–5 [37].

Acute rejection (AR) occurs at least once in 50 % of patients during the year [15, 37]. It usually occurs 10–14 days (minimum 5–7 days) after transplantation.

Pathogenetically: activation of T-cell and humoral factors with damage to the small parenchymal

vessels of the kidney, arteritis, microinfarcts, haemorrhages, and lymphocytic infiltration.

The clinical picture of AAR and AR is similar, differing only in the term of occurrence [8, 23, 37]. The complication is manifested by fever, weakness, loss of body weight, swelling and pain in the transplant area. Desensitization to the allograft may last up to one year and is corrected by immunosuppressive therapy.

Scintigraphically: a significant decrease in perfusion and parenchymal parameters, signs of active cortical retention [29].

Comparison of DRSG parameters in dynamics helps in the differential diagnosis of ATN and AR (Table 3) [29, 37], so experts recommend performing a baseline scintigraphic examination in the first 24–48 hours after transplantation [23, 31, 37].

Chronic allograft nephropathy (CAN, chronic rejection) is a slow, persistent process of damage to the transplanted kidney by immune complexes, which is the main cause of graft loss (30–80 %) [37]. The process is cumulative, irreversible, and cannot be treated. Risk factors: experienced severe ATN, episodes of acute rejection in the anamnesis, long-term therapy with calcineurin inhibitors [1].

Pathogenetically: chronic inflammation due to cellular and humoral damage, prolonged vasoconstriction with impaired intrarenal blood flow and subsequent fibrosis, tubular atrophy and glomerulosclerosis, gradually leading to cortical defects and progressive reduction of the amount of functioning parenchyma (reduction in the number of nephrons, formation of scars, thinning of the cortical layer and expansion of pyelocaliceal system) [1].

Scintigraphically: a moderate decrease in GFR, ERP, which can be the only sign of the beginning of the rejection process [15]. At further examinations there is a progressive deterioration of dynamic parameters and a reduction of cortical retention.

Immunosuppressant nephrotoxicity is a direct or indirect effect of chemicals or their metabolites, which leads to damage to the structural elements of the graft and a decrease in its functional capacity [37]. Cyclosporine has the greatest toxic potential (vasoconstrictive effect on the afferent arterioles of

the glomeruli), but today it is replaced by less toxic drugs (tacrolimus) [13, 15].

The scintigraphic pattern is non-specific and can be similar to ATN (rapid uptake and slow removal of radiopharmaceutical agents), but occurs later [23]; an acute cytotoxic reaction manifests itself in a similar way to AR (decreased perfusion and parenchymatous parameters, increased parenchymatous retention); the chronic nephrotoxic effect is similar to CAN (decrease in ERP and the amount of functioning parenchyma in dynamics) [15]. The results need to be correlated with the determination of cyclosporine levels, as this complication is dose-dependent.

Vascular complications related to surgical intervention

Vascular complications have a significant impact on life expectancy and effective graft functioning, occurring in about 10 % of recipients [4, 15, 37]. Early diagnosis and effective correction (especially surgical) significantly reduce the likelihood of severe complications and mortality. The golden standard of diagnosis is CT with angiography (clear determination of structural changes in vascular elements followed by angioplasty or stenting) [4, 15, 37].

A scintigraphic study with [^{99m}Tc] Tc-DTPA must necessarily include the flow phase for the purpose of quantitative and qualitative assessment [15].

Renal graft artery stenosis can occur above, below or at the level of the anastomosis due to perfusion damage to the graft, lack of vascular stitching, atherosclerotic changes in the donor vessels, turbulence in the blood flow at the perforation, kinking or compression of the artery in the wrong position. It develops within the first year after transplantation [4, 13, 15, 29].

It is clinically manifested by unexplained renal dysfunction, refractory arterial hypertension with vascular murmur over the transplant area. Ultrasound Doppler is an effective screening method [29].

The scintigraphic pattern looks like CAN pattern (follow up decrease in ERPF and the amount of functioning parenchyma). DRSG with ACE inhibitors is recommended to confirm the renovascular origin of hypertension [15].

Renal graft vein stenosis is a consequence of perivascular fibrosis and compression by perinephric fluid masses, which can be visualised scintigraphically [15].

Renal graft artery thrombosis is a critical irreversible early complication that leads to a heart

attack and subsequent loss of the graft, occurs in 0.5–2 % of cases [4, 15, 29]. Scintigraphically – lack of visualization of the graft in the flow and parenchymal phases.

Renal graft vein thrombosis occurs due to renal vein compression, surgical defects in the first week after surgery in 5 % of recipients [4, 15]; it leads to an infarct or bleeding due to the lack of draining collaterals. It is clinically manifested by sudden oliguria, pain and oedema in the graft area.

Scintigraphically, it is visualised as diffuse or focal reductions in radiopharmaceutical agent fixation in the graft tissue.

Non-vascular complications related to surgical intervention

Non-vascular complications include perinephric fluid masses (urinomas, haematomas, lymphocelles and abscesses), which occur in 50 % of renal transplant cases [4, 15]. The clinical significance of these masses is due to their size, localisation and tendency to grow further. Their danger increases if they become infected.

Each of these conditions has characteristic ultrasound signs.

Urinary leak or urinoma is a complication that occurs due to violations of graft extraction technique or the performance of ureterovesical anastomosis [4, 13, 15].

Pathogenetically: ischaemic necrosis of areas of the collecting system and increased urine pressure due to obstruction. Urinary extravasation can be of varying prevalence, occurring at any site of the urosepsis, more commonly the bowl of the kidney, the ureter, or the ureterovesical anastomosis [29].

It is clinically manifested by pain in the graft area, swelling of the legs, scrotum or labia, discharge from the postoperative wound, and a decrease in the amount of urine [29].

On ultrasound, it appears as a clearly delineated anechoic cavity without membranes, which increases rapidly [4, 15].

With DRSG, there is a progressive pathological accumulation of radiopharmaceutical agents in the areas of the leak, which do not fix the drug beforehand. Scintigraphic visualization helps in establishing the source of the leak and planning the intervention [4, 15, 32, 37].

Lymphocele of the graft bed is an area of lymphatic leakage from lymphatic ducts destroyed by iliac dissection or from the lymphatic vessels of the transplanted kidney, occurring in 10–15 % of cases. Risk factors are inadequate ligation of these ducts, heparin administration [4, 15].

Clinically, the course is asymptomatic, it appears by chance, but with a large volume it can compress the elements of the collecting system and cause hydronephrosis, lead to swelling of the legs, scrotum or labia [4, 15].

On ultrasound, it is a hypoechogenic rounded mass with membranes at the mid-ureter level [4, 15].

Scintigraphically, it is visualised as a photon-deficient area (which is a differential sign with urinoma), medial to the graft, between it and the bladder. The size and location of the mass does not change over the course of the examination or in delayed images [4, 15].

Haematoma occurs as a result of surgical intervention or spontaneously due to trauma or biopsy in 4–8 % of cases [29]. It is usually a small, sickle-shaped mass that resolves on its own. On ultrasound, a hyperechogenic mass is visualised [4, 15, 29].

Scintigraphically, it can be visualized during the perfusion phase immediately after its occurrence, but later – as a photon-deficient area.

Infection can complicate any condition, has no specific radiographic signs. About 80 % of recipients have infectious complications within a year after transplantation [4]. Clinically, they are manifested by fever, pain in the transplant area and signs of compression (in the case of an abscess).

Scintigraphically, it is manifested by a decrease in GFR and ERP in dynamics [4, 37].

Urinary tract obstruction is more often localised in the uretero-vesical region in secondary scarring due to ischaemia or rejection, when the ureter is kinked, compressed by perinephral fluid masses or due to technical errors during ureteroneocystectomy. It occurs in 2–5 % of cases [4, 13, 15, 29].

Clinically, the course is asymptomatic, since the denervation of the transplanted kidney eliminates the characteristic signs of renal colic, an increase in the level of serum creatinine indicates a functional impairment [4, 15, 29].

Ultrasound reveals nonspecific signs of expansion of the elements of the pyelocaliceal system.

Scintigraphically, it reveals characteristic signs of obstruction (enlargement of the calyx-pelvis complex, obstructive renogram) and determines the level of urinary tract obstruction. A test with furosemide helps to determine the recurrence of the obstruction [4, 15].

Prognostic significance of scintigraphy for renal transplant outcome

DRSG is a non-invasive method of determining the functional capacity of a transplanted kidney follow up, which allows to predict the occurrence of

complications and their impact on the renal graft outcome [37].

[^{99m}Tc] Tc-MAG3 is a drug of choice for evaluating graft function. It allows to determine ERPF – the main indicator of renal parenchyma dysfunction; also, this RPH provides a high-quality scintigraphic pattern due to its high extraction capacity [5, 6, 27].

Research with [^{99m}Tc] Tc-DTPA allows to obtain a high-quality angiographic curve, to detect and calculate the perfusion parameters more accurately [5, 6]. The value of various quantitative parameters for predicting renal graft outcome is a subject of many clinical studies [31, 33].

Kirchner's index is considered the best prognostic perfusion parameter for short-term assessment of the graft: its specificity is 99 % when predicting the first 3 months. A low Kirchner's index is a prognostic sign of graft loss within a year [20].

Hilson's index has prognostic value for 1-year and 5-year graft survival, especially in the presence of ATN, AR, vascular complications [26, 33, 27].

Graft index in DRSG with [^{99m}Tc] Tc-DTPA is considered a most accurate parameter for assessing delayed function and 1-year graft outcome in patients with a serum creatinine level greater than 1.5 mg/dL (sensitivity – 86.1 %, specificity – 86.2 %) [33]. Deterioration of graft function is accompanied by an increase in GI. With GI ≥ 5.5, the probability of dialysis in the first week after transplantation is 90.6 % [35].

B. Yazici et al. studied the values of perfusion and parenchymal parameters (perfusion peak time, accumulation index, renogram slope) to predict delayed graft function. The results correlated with biopsy data and Doppler parameters. According to the results of many studies, the prognostic value of these parameters was higher compared to the Doppler resistivity index (IR) [26, 33, 34, 36], however, none of the parameters made possible to distinguish ATN from AR [36]. These same parameters in DRSG with [^{99m}Tc] Tc-MAG3 were a statistically reliable predictor of 1-year graft outcome (for cadaveric grafts) [28]. Similar data confirming the sensitivity of kinetic parameters for predicting delayed graft function were obtained by other researchers [10, 11].

Perfusion and parenchymal kinetic parameters (T1/2 washout, ΔP and accumulation index) in DRSG with [^{99m}Tc] Tc-DTPA had prognostic value also for assessing long-term graft function (up to 5 years) [17, 34].

A high negative predictive level in predicting graft complications and life expectancy has normal kinetic parameters of the baseline DRSG (conducted in the early postoperative period) [22, 24].

Ardakani et al. proposed a multiparameter quantitative structural analysis of DRSG with [^{99m}Tc] Tc-DTPA. The sensitivity and specificity of the method is extremely high both for the diagnosis of AR (92.3 % and 96.3 %, respectively), and for the differential diagnosis of ATN and AR (88 % and 92.3 %, respectively) [7].

Quantitative assessment of the functioning of the transplanted kidney greatly facilitates the early diagnosis of possible complications and predicting the life span of the graft [6, 23].

Perspectives of the development of scintigraphic visualization in renal transplantology

Diagnostic imaging is of key importance for assessing functioning, identifying and predicting the course of possible complications of transplantation. Methods of radiation diagnostics, in particular nuclear medicine, are economically justified, low-cost, non-invasive and do not have a nephrotoxic effect [4, 15].

Additional possibilities open up when applying technologies of positron emission tomography (PET) combined with X-ray CT.

There is no conflict of interest.

Authors' participation: creation of the concept and draft of the article – M.S., M.Z.; collection of material, writing of the article – M.S., T.P., I.N.; text editing – M.S., M.Z., I.N.

Reference

- Zgrabian RO. Chronic renal allograft rejection: diagnosis, prevention, treatment (according to the conference materials). *Zdorovja Ukrainy [Health of Ukraine]* 2020; 4(21):14-5 (in Ukr).
- Lisovyi VM, Andonievna NM. Actual questions of kidney transplantation: a study guide for interns. Kharkiv: KhNMU; 2013. 184 p (in Ukr).
- Novytska M. The main changes to the legislation of Ukraine in the field of transplantation of anatomical materials to humans. *Administratyvne pravo i process [Administrative Law and Process]*. 2018;9:132-7 (in Ukr).
- Akbar SA, Jafri SZ, Amendola NA, Madrazo BL, Salem R, Bis KG. Complications of renal transplantation. *Radiographics*. 2005;25(5):1335-56. doi: 10.1148/rg.255045133.
- Aktaş A, Aras M, Colak T, Gençoğlu A, Karakayali H. Comparison of Tc-99m DTPA and Tc-99m MAG3 perfusion time-activity curves in patients with renal allograft dysfunction. *Transplant Proc*. 2006;38(2):449-53. doi: 10.1016/j.transproceed.2006.01.006.
- Aktaş A. Transplanted kidney function evaluation. *Semin Nucl Med*. 2014;44(2):129-45. doi: 10.1053/j.semnuclmed.2013.10.005.
- Ardakani AA, Hekmat S, Abolghasemi J, Reiazi R. Scintigraphic texture analysis for assessment of renal allograft function. *Polish J Radiol*. 2018;83:e1–10. doi: 10.5114/pjr.2018.74956.
- Benjamens S, Berger SP, Glaudemans AWJM, Sanders JSF, Pol RA, Slart RHJA. Renal scintigraphy for post-transplant monitoring after kidney transplantation. *Transplant Rev (Orlando)* 2018;32(2):102-9. doi: 10.1016/j.trre.2017.12.002.
- Benjamens S, Moers C, Slart RHJA, Pol RA. Kidney transplantation and diagnostic imaging: The early days and future advancements of transplant surgery. *Diagnostics*. 2021;11(1):1-10. doi: 10.3390/diagnostics11010047.
- Benjamens S, Pol RA, Berger SP, Glaudemans AWJM, Dibbets-Schneider P, Slart RHJA, De Geus-Oei LF. Limited clinical value of two consecutive post-transplant renal scintigraphy procedures. *Eur Radiol*. 2020;30(1):452-60. doi: 10.1007/s00330-019-06334-1.
- Benjamens S, Pol RA, De Geus-Oei LF, De Vries APJ, Glaudemans AWJM, Berger SP, Slart RHJA. Can transplant renal scintigraphy predict the duration of delayed graft function? A dual center retrospective study. *PLoS One*. 2018;13(3):1-13. doi: 10.1371/journal.pone.0193791.
- Blafox MD, De Palma D, Taylor A, Szabo Z, Prigent A, Samal M, Li Y, Santos A, Testanera G, Tulchinsky M. The SNMMI and EANM practice guideline for renal scintigraphy in adults. *Eur J Nuclear Medicine and Molecular Imaging*. 2018;45:2218-28. doi: 10.1007/s00259-018-4129-6.
- Boubaker A, Prior JO, Meuwly JY, Bischof-Delaloye A. Radionuclide investigations of the urinary tract in the era of multimodality imaging. *J Nucl Med*. 2006;47(11):1819-36.
- Breda A, Budde K, Figueiredo A et al. EAU Guidelines on

- Renal Transplantation // European association of Urology 2022. URL: <https://docslib.org/doc/11702301/eau-guidelines-on-renal-transplantation>.
15. Brown ED, Chen MJM, Wolfman NT, Ott DJ, Watson NE. Complications of Renal Transplantation: Evaluation with US and Radionuclide Imaging. *RadioGraphics*. 2000;20:607-22.
 16. Castellucci P, Deandrei D, Krizsán AK, Mirzaei S, Prior J, Sattler B. A joint publication by EANM and UEMS/EBNM. Nephro-urinary. European Nuclear Medicine Guide. URL: <https://www.nucmed-guide.app/#!/toc/309>.
 17. Chong A, Ha JM, Choi NK, Shin MH. Using post transplant 1 week Tc-99m DTPA renal scan as another method for predicting renal graft failure. *Open Med*. 2019; 14(1):509–515. doi: 10.1515/med-2019-0056.
 18. Damasio MB, Muller L-SO, Piaggio G, Marks SD, Riccabona M. Imaging in pediatric renal transplantation. *Pediatric Transplantation* 2017;21:e12885. doi: 10.1111/ptr.12885.
 19. Derlin T, Gueler F, Bräsen JH, Schmitz J, Hartung D, Herrmann TR, Ross TL, Wacker F, Wester H-Y, Hiss M, Haller H, Bengel FM, Hueper K. Integrating MRI and Chemokine Receptor CXCR4-Targeted PET for Detection of Leukocyte Infiltration in Complicated Urinary Tract Infections After Kidney Transplantation. *J Nucl Med*. 2017;58:1831-7. doi: 10.2967/jnumed.117.193037.
 20. Guignard R, Mourad G, Mariano-Goulart D. Utility of post-surgical renal scintigraphy to predict one-year outcome of renal transplants in patients with delayed graft function. *Nucl Med Commun*. 2011;32(4):314-9. doi: 10.1097/MNM.0b013e3283446297.
 21. Guignard R, Mourad G, Mariano-Goulart D. Utility of post-surgical renal scintigraphy to predict one-year outcome of renal transplants in patients with delayed graft function. *Nucl Med Commun*. 2011;32(4):314-9. doi: 10.1097/MNM.0b013e3283446297.
 22. Heaf JG, Iversen J. Uses and limitations of renal scintigraphy in renal transplantation monitoring. *Eur J Nucl Med*. 2000; 7(7):871-9. doi: 10.1007/s002590000281.
 23. Khor YM, Lam WWC, Wong WY, Goh ASW. Role of Nuclear Medicine Imaging in Evaluation of Complications Following Renal Transplant. *Proceedings of Singapore Healthcare*. 2015;24(4): 233-42. doi: 10.1177/2010105815611813.
 24. Lee SF, Lichtenstein M, Hughes P, Sivaratnam D. Utility of MAG3 scintigraphy with the use of a 2 min uptake parameter in the assessment of postsurgical renal transplant complications. *Nucl Med Commun*. 2018;39(10):921-7. doi: 10.1097/MNM.0000000000000885.
 25. Lovinousse P, Weekers L, Pottel H, Bouquegneau A, Bonvoisin C, Bovy C, Grosch S, Hustinx R, Jouret F. [¹⁸F] FDG PET / CT imaging disproves renal allograft acute rejection in kidney transplant recipients with acute kidney dysfunction: a validation cohort. *Eur J Nucl Med Mol Imaging*. 2021;331-5. doi: 10.1007/s00259-021-05467-0.
 26. Ngai S, Demetriades T. Prediction of Long-Term Renal Transplant Allograft. *Clin Nucl Med*. 2008;33(2):102-5. doi: 10.1097/RLU.0b013e31815f2468
 27. Park UJ, Kim HT, Cho WH, Kim MY, Hwang EA, Han SY, Park SB, Kim HC, Zeon SK. Use of Early Postoperative MAG3 Renal Scan To Predict Long-Term Outcomes of Renal Transplants. *Exp Clin Transplant*. 2013;118-21. doi: 10.6002/ect.2012.0090
 28. Russell CD, Yang H, Gaston RS, Hudson SL, Diethelm AG, Dubovsky EV. Prediction of Renal Transplant Survival from Early Postoperative Radioisotope Studies. *J Nucl Med*. 2000;41(8):1332-6.
 29. Sharfuddin A. Renal relevant radiology: Imaging in kidney transplantation. *Clin J Am Soc Nephrol*. 2014;9(2):416-29. doi: 10.2215/CJN.02960313.
 30. Taffel MT, Nikolaidis P, Beland MD, Blaufox MD, Dogra VS, MDe, Goldfarb S, Gore JL, Harvin HJ, Heilbrun ME, Heller MT, Khatri G, Preminger GM, Purysko AS, Smith AD, Wang ZJ, Weinfeld RM, Wong-You-Cheong JJ, Remer EM, Lockhart ME. ACR Appropriateness Criteria Renal Transplant Dysfunction. *J Am Coll Radiol*. 2017;14(5S):272-81. doi: 10.1016/j.jacr.2017.02.034
 31. Volkan-Salanci B, Erbas B. Imaging in Renal Transplants: An Update. *Semin Nucl Med*. 2021;51(4):364-79. doi: 10.1053/j.semnuclmed.2020.12.011
 32. Yazici B, Oral A, Akgün A. Contribution of SPECT/CT to Evaluate Urinary Leakage Suspicion in Renal Transplant Patients. *Clin Nucl Med*. 2018;43:e378-e380. doi: 10.1097/RLU.0000000000002222.
 33. Yazici B, Oral A, Gokalp C, Akgün A, Toz H, Hoscoskun C. A new quantitative index for baseline renal transplant scintigraphy with ^{99m}Tc-DTPA in evaluation of delayed graft function and prediction of 1-year graft function. *Clin Nucl Med*. 2016;41(3):182-8. doi: 10.1097/RLU.0000000000001020.
 34. Yazici B, Oral A, Gokalp C, Akgün A, Toz H, Ozbek SS, Yazici A. Evaluation of renal transplant scintigraphy and resistance index performed within 2 days after transplantation in predicting long-term graft function. *Clin Nucl Med*. 2015;40(7):548-52. doi: 10.1097/RLU.0000000000000078.
 35. Yazici B. Practical method for calculation of graft index in renal transplant scintigraphy: A technical note. *Clin Nucl Med*. 2019;44(1):32-7. doi: 10.1097/RLU.0000000000002330.
 36. Yazici B, Yazici A, Oral A, Akgün A, Toz H. Comparison of renal transplant scintigraphy with renal resistance index for prediction of early graft dysfunction and evaluation of acute tubular necrosis and acute rejection. *Clin Nucl Med*. 2013;38(12):931-5. doi: 10.1097/RLU.0000000000000271.
 37. Ziessman HA, O'Malley JP, Thrall JH. Nuclear medicine: the requisites. 4th edition. Elsevier; 2013. 464 p.

М.В. Сатир, І.В. Новерко, Т.І. Пантус, М.С. Загрійчук

ДУ «Інститут серця МОЗ України», Київ

Значення методів ядерної медицини для діагностики і прогнозування перебігу ускладнень трансплантації нирки

Трансплантація нирки – це метод замісної терапії термінальної ниркової недостатності, заснований на між-дисциплінарній співпраці науковців і клініцистів, поєднанні здобутків хірургії, імунології та променевої діагностики. Після трансплантації можуть виникати ускладнення, пов'язані зі станом трансплантата, імунологічними факторами сумісності донора і реципієнта та хірургічним утручанням. Рання діагностика та своєчасне лікування ускладнень важливе для оцінки і прогнозу функціонування трансплантата.

У статті розглянуто ускладнення трансплантації нирки: причини їхнього виникнення, патогенез, клінічну картину та ознаки, що виявляються за допомогою візуалізації. Проаналізовано можливості променевих методів для диференційної діагностики прехірургічних, нехірургічних ускладнень і таких, що пов'язані з хірургічним утручанням.

Основну увагу приділено ядерній медицині, а саме динамічній реносцинтиграфії (ДРСГ) як методу визначення функціонального стану трансплантата. Це безпечний широкодоступний неінвазивний метод оцінки якісних і кількісних параметрів функціонування нирки. ДРСГ послідовно характеризує перфузію, екстракцію та екскрецію у досліджуваному органі. У статті наведено стандартний протокол ДРСГ з ^{99m}Tc Tc-MAG3 та ^{99m}Tc Tc-DTPA, переваги і недоліки сцинтиграфії з цими радіофармпрепаратами (РФП). Описано сцинтиграфічні ознаки різних ускладнень. Проаналізовано дослідження кінетичних перфузійних і паренхіматозних параметрів ДРСГ та їхнє значення для диференційної діагностики ускладнень, відстроченої і уповільненої функції трансплантата, оцінки короткотривалого та довготривалого його функціонування. Акцентовано на прогностичній значущості змін ДРСГ у динаміці.

Розглянуто перспективи подальшого розвитку методів сцинтиграфії для оцінки стану трансплантованих нирок із впровадженням високоякісної тривимірної візуалізації, новітніх РФП. Зроблено висновки про важливість ядерної медицини як елемента мультидисциплінарного підходу в трансплантології.

Ключові слова: ускладнення трансплантації нирок, динамічна реносцинтиграфія, сцинтиграфічні кінетичні перфузійні і паренхіматозні функціональні параметри.