ELSEVIER

Seminars in
NUCLEAR
MEDICINE

Imaging in Renal Transplants: An Update

Bilge Volkan-Salanci, MD, PhD* and Belkis Erbas, MD†

Renal transplantation has become the best treatment for the patients with chronic renal insufficiency. The surgical procedures, immunosuppressive regiments and patient follow-up have evolved especially in the last 10 years. However, the diagnosis for renal transplantation dysfunction remained the same in these years. Serum creatinine levels and estimated glomerular filtration rate calculated by serum creatinine based equations are used in routine patient follow-up. Pelvic ultrasonography and color Doppler ultrasonography are used as a first-line imaging method. Assessment of allograft functions both qualitatively and quantitatively are possible using nuclear medicine procedures. Surgical complications, acute tubular necrosis, subacute and/or acute rejection, infections, toxicity due to immunosuppressive medications, complications relating the collecting system, chronic rejection are the main causes for renal function impairment. The imaging procedures can diagnose the worsening of renal transplant function; however, they still lack the ability to differentiate types of rejection as histopathology or differentiate rejection from other causes of allograft dysfunction. The transplant biopsy gives detailed diagnosis for allograft dysfunction, guide the treatment and therefore it is the preferred diagnostic choice in recent years. On recent years, literature on radionuclide imaging is focused on perfusion analysis for the early diagnosis of renal transplant dysfunction and prognostic use of perfusion parameters, and then this article will focus on these studies and their outcome.
Semin Nucl Med 51:364-379

Introduction

The history of renal transplantation began with Emerich Ullman in early 1900s when he performed the first autograft and the first xenograft.[1] However, the attempts of human allografts were unsuccessful with the few exceptions of renal transplantations between identical twins, until the use of immunosuppressive drugs by Tom Starzl in 1963.[2] As the patient management and use of immunosuppressive drugs improved, first dynamic radionuclide studies were performed using I-131 iodrast and I-131 Hippuran in 1963-1964, which was followed by scintigraphies using Tc-99m Diethylenaminepentaacetic acid (DTPA).[3] Several radiopharmaceuticals have been used for the measurement of renal blood flow and glomerular flitration rate levels using multiple plasma sampling or single sampling formulas, such as I-131-OIH, Cr-51-EDTA, I-125-Iothalamate and Tc-99m DTPA.[4,5] The attempt of quantification for the differential diagnosis between acute tubular necrosis (ATN) and rejection in transplant patients was made by others.[6,7] In 1986, Tc-99m mercapto acetyl triglycine (MAG3) was introduced and first used in renal transplant patients.[8] It has become the first choice radiopharmaceutical in some centers because of high first pass extraction and better imaging quality.[9] Tc-99m MAG3 clearance was proposed for effective renal plasma flow estimation.[10,11] In addition, other tubular agents such as Tc-99m ethylenedicysteine (EC) were introduced.[12] A baseline dynamic renal scintigraphy (DRS) can be performed to document baseline renal transplant function routinely or if delayed graft function (DGF) is observed. Although widely used in 1990s and in early 2000s, after worldwide use of Doppler ultrasound (US), the European Association of Urology guidelines do not recommend the routine use of DRS for the evaluation of renal function in renal transplants.[13] However, especially on pediatric population, use of DRS with Tc-99m MAG3 is encouraged to assess excretory function or for suspicion of urinary leakage of renal transplant.[9] The imaging procedures can diagnose the worsening of renal transplant function; however, they still lack the ability to differentiate

*Assoc Prof. Dept. of Nuclear Medicine, Hacettepe University, Medical School, Ankara, Turkey.
†Prof. Dept. of Nuclear Medicine, Hacettepe University, Medical School, Ankara, Turkey.
Address reprint requests to Belkis Erbas MD, Professor of Nuclear Medicine, Department of Nuclear Medicine, Medical School, Hacettepe University, Sıhhiye, Altindag 06100, Ankara, Turkey. E-mail: belkis.erbas@gmail.com

 https://doi.org/10.1053/j.semnuclmed.2020.12.011
0001-2998/

types of rejection as histopathology or differentiate rejection from other causes of allograft dysfunction.

The transplant biopsy gives detailed diagnosis for allograft dysfunction, guides the treatment and therefore is the preferred diagnostic choice in recent years.[13] In 1991, in Bannf-Canada, a standardized classification of transplant biopsies was reported, and these international standards have been modified in every 2-years. In Banff classification, the adequacy of the biopsy specimen is defined and the histopathologic changes such as glomerulitis, tubulitis, interstitial fibrosis, arteritis, arterial hyalinosis or interstitial inflammation are scored based on severity, and a final diagnosis is assigned to one of the six categories.[14] These categories include normal findings, which exclude the diagnosis of rejection or other pathologies such as infection. Rejection, if present, is classified as antibody mediated rejection (category 2), "borderline category" which is defined as suspicious for T cell mediated rejection, or T cell mediated rejection. Other main categories include tubular atrophy-interstitial fibrosis and other causes such as viral infections, calcineurin toxicity, post-transplant lymphoproliferative disorder, etc.[14] The clinicians manage the treatments according to this detailed histopathologic classification.[13] The most recent meeting, the XV. Banff conference, was held in Pittsburgh, Pennsylvania, USA in 2019. The meeting report defined active and inactive scores for both for antibody-mediated rejection and T cell mediated rejection. The main categories are listed in Table 2. [15]

After successful kidney transplantation, the transplant patients are followed meticulously in order to diagnose allograft dysfunction early. The patients may experience tenderness or sometimes swelling at the graft site. The estimated glomerular filtration rate may decrease and serum creatinine levels may increase. Change in urine output may be a possible presentation in these patients. Non-renal causes might be responsible for allograft dysfunction, such as drugs (nonsteroidal anti-inflammatory drugs, angiotensin receptor blockers, or angiotensin converting enzyme inhibitors), hypercalcemia, hypovolemia, or increased vasodilatation due to sepsis. However, the scope of this review is the identification of the renal or post renal causes of allograph dysfunction (Table 1).

Table 1 Complications of Renal Transplant Patients

- a **Complications related to surgery**
  - a Vascular complications
    - i Renal artery
    - ii Renal vein
  - b Non-vascular complications
    - i Perinephric collections
      - 1 Hematomas
      - 2 Urinomas
      - 3 Lymphoceles
      - 4 Abscess
    - ii Urinary strictures
- b **Non-surgical complications**
  - a Complications related to allograft function
    - i Acute tubular necrosis
    - ii Acute rejection
    - iii Immunosuppressive drug toxicity
    - iv BK virus infection
    - v Chronic rejection

Renal Transplant Dysfunction

Early transplant dysfunction may be a result of hyperacute rejection due to preformed antibodies in the recipient. The morphological change is usually observed even during the operation; therefore, no imaging is necessary, in general.

The term DGF is used when the patient needs hemodialysis in the following week of transplantation.[16] Presence of DGF is strongly related to operational factors such as both warm ischemia time and cold ischemia time.[16] In the post-surgical period, surgical complications, such as renal artery and/or venous thrombosis, renal artery stenosis, hematoma, might be the reasons of early renal dysfunction.[17] Many other factors that are related to either donors or recipients are also present and discussed in detail elsewhere.[16] DGF is a bad prognostic factor, because episodes of acute rejection are more frequent and allograft survival is shorter for patients who experienced DGF.[18,19] ATN is the most common cause of DGF reported on histopathologic examination. Antibody related rejection, cortical necrosis and endothelial damage are the other frequently reported causes of DGF.[19,20] Whatever the cause, DGF stimulates an innate immune reflection in the allograft, with the release of cytokines such as interleukin 1, interleukin 6, tumor necrosis factor alpha and interferon beta. DGF activates immune cells, triggers the antigen reactive T-cell response, and therefore increases the immunogenicity of the allograft.[18] Wu *et al* followed a cohort of 654 patients over 12 years and showed that allograft rejection risk is increased 1.64 fold in patients with DGF.[21] They showed

Table 2 Changes in Banff Diagnostic Categories, in 2019, Modified From [15]

Bannf Categories		
Category 1	Normal or non-specific changes	
Category 2	Antibody mediated changes	Active antibody mediated rejection
		Chronic active antibody mediated rejection
		Chronic (inactive) antibody mediated rejection
		C4d staining without evidence of rejection
Category 3	Suspicious for T cell mediated rejection (borderline)	
Category 4	T cell mediated rejection	Acute T cell mediated rejection (Grade I-III)
		Chronic active T cell mediated rejection (Grade I-II)
Category 5	Polyomavirus nephropathy	Grade I
		Grade II
		Grade III

that both antibody related rejection and T-cell mediated rejection were seen in patients with DGF with a hazard ratio of 1.54 and 1.52, respectively.[21]

a. ATN:

ATN is the most common cause of DGF and is a result of ischemia followed by reperfusion injury. It is related to cold and warm ischemia time, and spontaneous recovery is generally expected.[22] ATN also can be seen in the long-term follow up if the patients experience volume depletion or hypotension due to diarrhea, vomiting, dehydration (Fig. 1).

b. Subclinical Acute Rejection and/or Acute Rejection:

Acute rejection can be antibody mediated or T cell mediated and may be seen in every transplant patient at any time point. Early detection and management of rejection prolongs the survival of the allograft.[22]

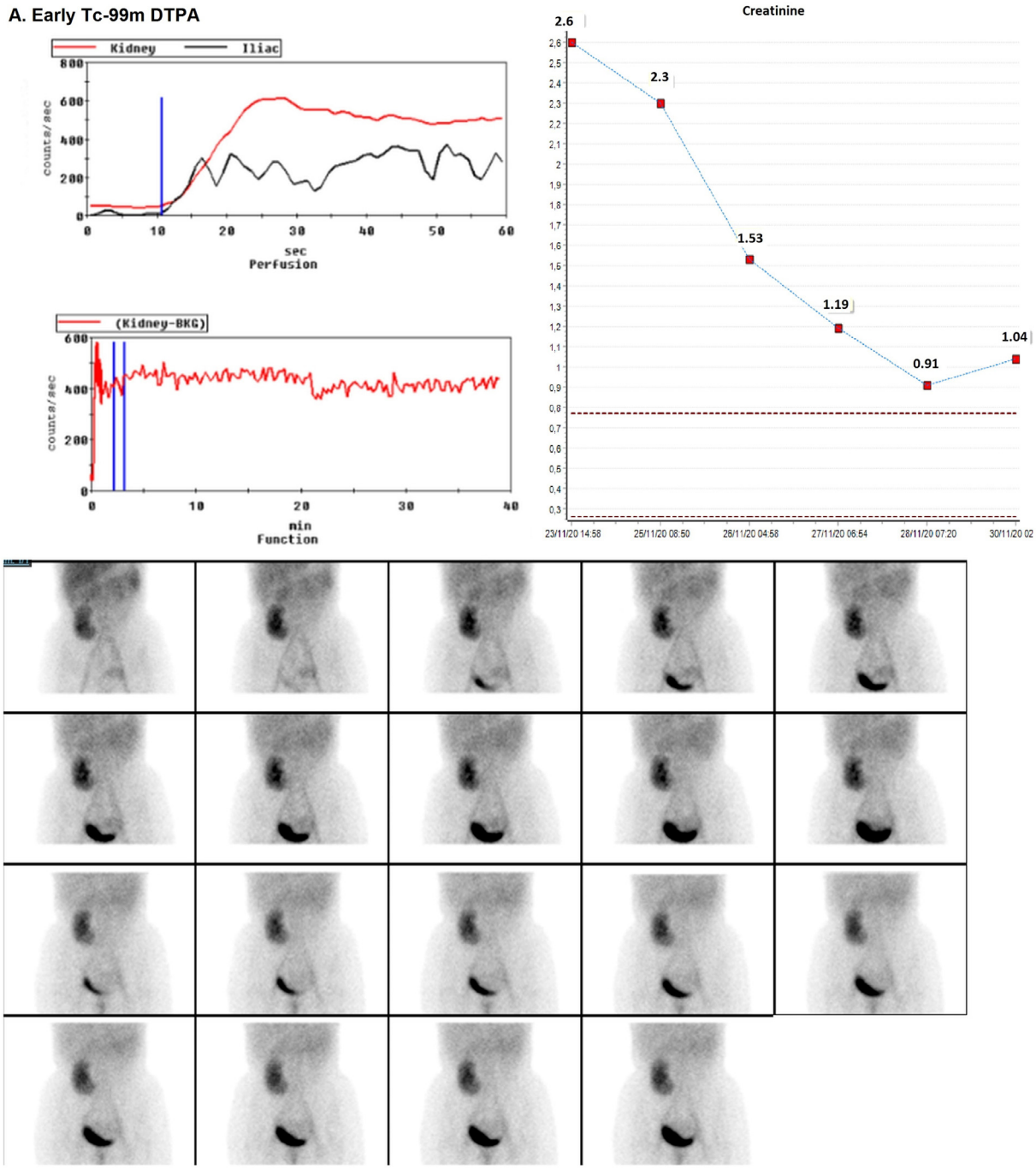

Figure 1 Sixteen-year-old female patient was admitted to hospital with nausea and vomiting. The patient had serum creatinine elevation (A) (up right graphic). Tc-99m DTPA scan revealed decreased perfusion and impaired function. The patient was correctly hydrated, the creatinine was 0.9 mg/dL and a control Tc-99m DTPA DRS was performed showing a better function curve (B) within 3 days.

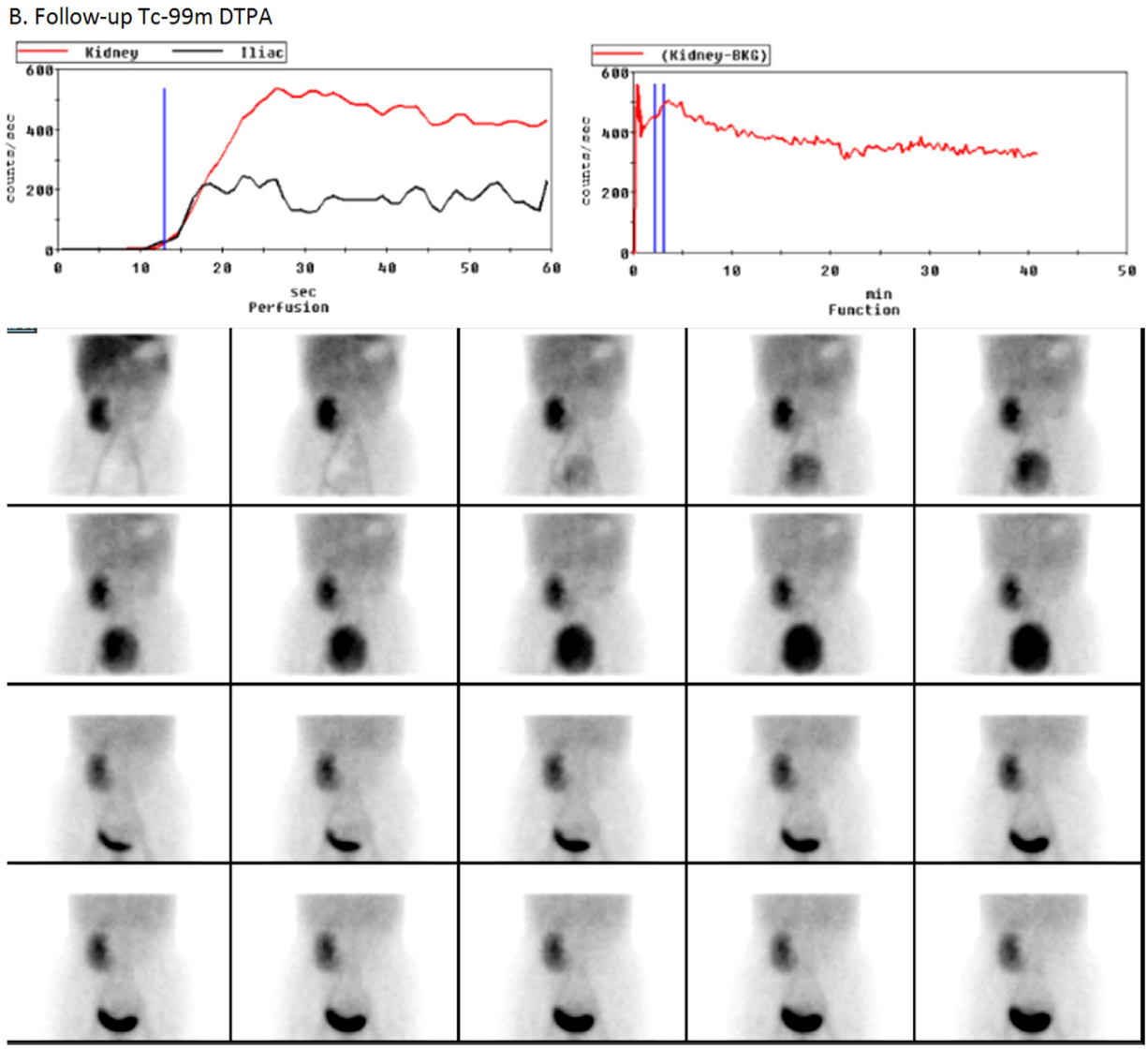

Figure 1 Continued.

c. Chronic Rejection

Antibodies mediate chronic rejection and the result is glomerulosclerosis generally diagnosed by sequential biopsies. Chronic rejection is progressive and has poor prognosis.

d. Infection

Nosocomial infections are the common cause of infection in the early post-transplant period. However, in long-term BK virus, which is a member of polyomavirus family, generally cause infections. The virus stays latent in genitourinary cells after the first episode of infection; therefore, periodic viral load screening is performed on regular basis.[22]

e. Complications Related to Collecting System

Non vascular complications of renal transplantation include urine leaks and obstruction of the ureter. Urinary leaks and ureter obstruction related to surgical technique usually occur early in the post-transplant period up to 1 month.[22] Obstruction due to strictures or ischemia are usually seen in the first 6 months.[23] However, ureter obstruction can be seen any time in the survival of the transplant. US generally reveals dilated collecting system, but noninvasive assessment of both urinary leaks and obstruction is possible using DRS.

f. Complications Related to Immunosuppressive Medication

Immunosuppressive medications such as cyclosporine and tacrolimus may cause arteriolar vasoconstriction resulting in decrease in GFR and increase in serum creatinine levels.

Renal Ultrasonography

Transplant centers perform early post-transplant period and pelvic US with color Doppler US as first line imaging.[13] Renal US has several advantages such as bed-side imaging, lack of irradiation and non-invasiveness especially in pediatric population.[9] Perfusion indices of main renal and intrarenal arteries

can be calculated; change of parenchymal echogenicity can be monitored. It can be used to monitor physiological changes that are present in the first days of transplants, such as thickening of collective system and renal hypertrophy seen in the first months. Resistivity index (RI) is one of the perfusion indices and show vascular resistance, and is a strong predictor of renal dysfunction. However, it is not specific and cannot differentiate the causes of dysfunction.[24] US helps to evaluate the patency of renal artery and vein, integrity of renal ureteral anastomosis; it diagnoses post-surgical hematomas, infection or other fluid collections (Table 1). In the long term, US is used in the patient follow-up routinely, and late complications such as ureteral strictures can also be diagnosed.

Imaging in Nuclear Medicine

Functional imaging has two approaches to renal transplants. The first is to monitor the functional changes of the renal transplant, which is mainly covered by DRS. DRS evaluates perfusion, concentration and excretion function of transplant kidneys both qualitatively and quantitatively. DRS lacks anatomical resolution; however, as any functional imaging does, it has the ability to predict either short-term or long-term outcome. Earliest change in renal function is the elevation of serum creatinine levels and decrease in GFR. In addition to imaging, nuclear medicine allows monitoring measured GFR using Cr-51 EDTA or using Tc-99m DTPA by simplified formulas.[4,5] Measured GFR is accepted as a more accurate parameter compared to routinely used estimated GFR values based on plasma clearance levels. The second approach is to image rejection itself using radiopharmaceuticals of inflammation such as F-18 FDG or radiolabelled leucocytes. This is a direct but more affective approach. Imaging the inflammation not only makes the diagnosis the rejection but also interprets the severity.

Nuclear Medicine Procedures to Assess Allograft Function

a. Dynamic renal scintigraphy

DRS has a well-defined acquisition protocol in renal transplant patients. Dynamic images are acquired from anterior projection by positioning the gamma camera detector on renal allograft. Immediately after injection of the radiopharmaceutical, dynamic images of three phases are acquired. Hydration of the patient and a detailed history is essential before DRS to reveal proper transplant functioning (Fig. 1). The first phase of the radionuclide renogram is the flow phase and is essential for evaluation of the perfusion function of allograft. From the perfusion images, time activity curves are generated by drawing regions of interest on allograft, abdominal aorta or iliac arteries.[25] Perfusion indices generated from first phase are listed in Table 3. Gupta *et al* compared the use of both aorta and iliac arteries for calculating perfusion indices such as Hilsons's index, Kirchner's index,

Table 3 Semi-quantitative Parameters of Dynamic Renal Scintigraphy

Perfusion Parameter	Definition	Reference
Hilson's index	Area under vascular perfusion curve to peak/ area under allograft perfusion peak	6
Time to Ppeak	Time to perfusion peak	
ΔP	Time difference between time to perfusion peak of allograft and aorta	
Kirchner's index	ratio of the mean upstroke portions of the kidney and aortic curves	27
P:PI	Peak counts/plateau counts	
Graft washout T1/2	T1/2 of perfusion peak downslope curve	28
The graft/aorta perfusion ratio	Allograft peak perfusion counts/ aorta peak perfusion counts	29
Slope of second phase perfusion	Slope of second phase perfusion 30-60 sec	30
Graft index	Perfusion and function of allograft in first 3 min. ΔP x (cAxcPI) /(cPxcU3)*.	31

Parenchymal functions (extraction and excretion) Parameter	Definition	Reference
Peak Perfusion/ Peak uptake	Peak perfusion counts/ Peak uptake	
Tmax	Time to reach peak activity	32
2MU	Uptake of MAG3 at 2 min	33
T1/2	Half time of renal excretion	
Retention (R20)	Activity of renal parenchyma at 20 min / peak activity	
R20/3	Accumulation index Counts of 20 min/counts of 3 min	32,34

* ΔP: difference of peak perfusion counts of allograft and iliac artery
cA: peak perfusion counts of iliac artery
cPI: perfusion plateau of allograft
cP: peak perfusion counts of allograft
U3: total uptake at 3 min

ΔP and kidney to arterial ratio, and they showed that repeated interobserver calculation of perfusion parameters were better using iliac arteries, most probably because there is less soft tissue attenuation.[26]

Both Tc-99m DTPA and Tc-99m MAG3 radiopharmaceuticals are used in assessment of renal allografts' function after transplantation. Tc-99m DTPA is filtrated through glomerulus, allowing the measurement of GFR. Higher doses are used in DRS generating a better bolus injection. The perfusion curve of Tc-99m DTPA is defined as a rapid increase to a perfusion peak, rapid decrease and a plateau phase, which is followed by a concentration peak (Fig. 2).[25] Many perfusion parameters are derived from this perfusion peak of Tc-99m DTPA (Table 3). Tc-99m MAG3, the other most frequently used radiopharmaceutical in renal transplant patients, has a high extraction via organic anion transporters, which are highly expressed in the proximal tubules; therefore, better quality images are acquired.[35] Tc-99m MAG3 was proposed as the radiopharmaceutical of choice especially in patients with decreased renal function.[36] The perfusion curve of renal transplant has first pass peak followed by a second peak showing early tubular extraction (Fig. 3). It was shown that this second peak was flattened in graft rejection.[37,38] Recent publication favors Tc-99m DTPA over Tc-99m MAG3 in renal transplant patients due to various perfusion parameters that detect change of function.[25] Comparison of 2 radiopharmaceuticals was done in 28 transplant patients by Ayaz *et al* and Hilson's index and R20/3 were found to be similar in both.[37] When perfusion and functional parameters are assessed together for the detection of worsening allograft function, Tc-99m DTPA showed increased sensitivity (75%) over Tc-99m MAG3 (57.1%).[37] On DRS preserved perfusion with decreased Tc-99m DTPA uptake and excretion of the radiopharmaceutical is the main finding, that is used to differentiate ATN from rejection (Fig. 2). If the Tc-99m MAG3 is used, due to impaired urinary flow, cumulative parenchymal retention of the radiotracer is observed.

The parameter that has highest sensitivity for Tc-99m DTPA studies were reported to be peak to plateau ratio which was more sensitive when compared to Hilson's index. It was the first parameter that worsened in graft dysfunction.[37] Gupta *et al* reported that higher Hilson's index values showed a kidney pathology either ATN, vascular rejection or renal vascular compromise, while lower values were seen in interstitial rejection or normal kidneys.[26] They concluded that Hilson's index is the best parameter to assess graft function.[26] Hilson's index can also be applied to Tc-99m MAG3 RDS. Ngai *et al* showed that Hilson's index can successfully differentiate normal functioning grafts, from impaired function, however cannot differentiate between etiologies.[39] Hilson's index was shown to predict allograft outcome at the end of first year and fifth year, and it was more sensitive than RI of US.[39,40] The threshold used in the studies were different. If the threshold was increased from 100 to 278, specificity was increased from 54%, to 78%, as well.[26,39,40]

DGF when present on the first week of renal transplantation, it is shown to be related to shortened graft survival (Fig. 4). Guignard *et al* analyzed the results of DRS using Tc-99m MAG3 within 72 hours in the post-transplant period in 100 patients with the diagnosis of DGF. They reported that Kirchner perfusion index was the best predictive index among all the perfusion parameters.[41] Ratio of graft perfusion to perfusion of aorta had the highest sensitivity, and Kirchner's index was highly specific (99%) in predicting allograft function in first 3 months with a low sensitivity (30%). Low Kirchner index values were associated with transplantation failure at first year.[41] A major limitation in this study is the lack of biopsy confirmation.[41]

Graded perfusion curves of 104 baseline DRS's and 46 follow-up DRS studies' and RI of Doppler US were correlated with patients' biopsies.[42] Both parameters of perfusion successfully predicted both slow graft function and DGF, and have better performance than RI of Doppler US especially in slow graft function. None of the parameters could differentiate ATN from acute rejection.[42] Downslope of the perfusion curve was also assessed in the literature and T1/2 of the downslope curve as one of them.[42] Although not measured directly, this parameter somehow is related to perfusion curve grading. T1/2 of the perfusion peak was higher in both ATN and acute rejection when compared to normal graft function. Time period of this downslope (GW1/2) was also measured by Yazıcı *et al* and prolonged GW1/2 more than 28 sec related to rejection; although, this was not supported in the literature.[42] Tubular function slope measured by Guinard *et al* was also a parameter that accounts T1/2, and they showed that it is an independent prognostic parameter for graft survival.[41]

Benjamens *et al* graded the time activity curve of uptake and excretion of Tc-99m MAG3, and showed that higher the grade on the first 3 days, longer the patients' need for dialysis, and high grade curves predict the longer hospital stays with a hazard ratio of 1.8.[43] Time activity curve grade using Tc-99m DTPA also predicted graft function at 1st year and at the end of 5th year and found to be a better predictor when compared to resistivity index of Doppler US.[24] However, other quantitative parameters such as tubular uptake, corrected TER or uptake at 10 min. did not show significance on multivariate analysis for predicting prolonged hospital stay.[43] Uptake of Tc-99m MAG3 at 2 min. was measured as the ratio of 2 min. uptake to injected dose and given as percent uptake.[33] A negative correlation was reported between 2 min. Tc-99m MAG3 uptake and serum creatinine levels at third month.[33] Parameters evaluating graft's uptake function (Table 3) are also used to differentiate ATN from acute rejection. Lee *et al* correlated uptake of Tc-99m MAG3 at 2 minutes for DRS that were performed within 96 h after transplantation.[33] They reported that a good perfusion has a high negative predictive value of 79%-89%, but dynamic scintigraphy using Tc-99m MAG3 had low specificity in differentiating acute rejection from ATN.[33] The authors showed a negative correlation between uptake at 2 min. and serum creatinine levels at the end of third month and 1 year.[33] Perfusion and uptake parameters' ability to foresee the duration of DGF was tested, and the authors showed that corrected TER and average upslope had high sensitivity and specificity for the prediction DGF duration.[44] Yazıcı *et al* tested excretion

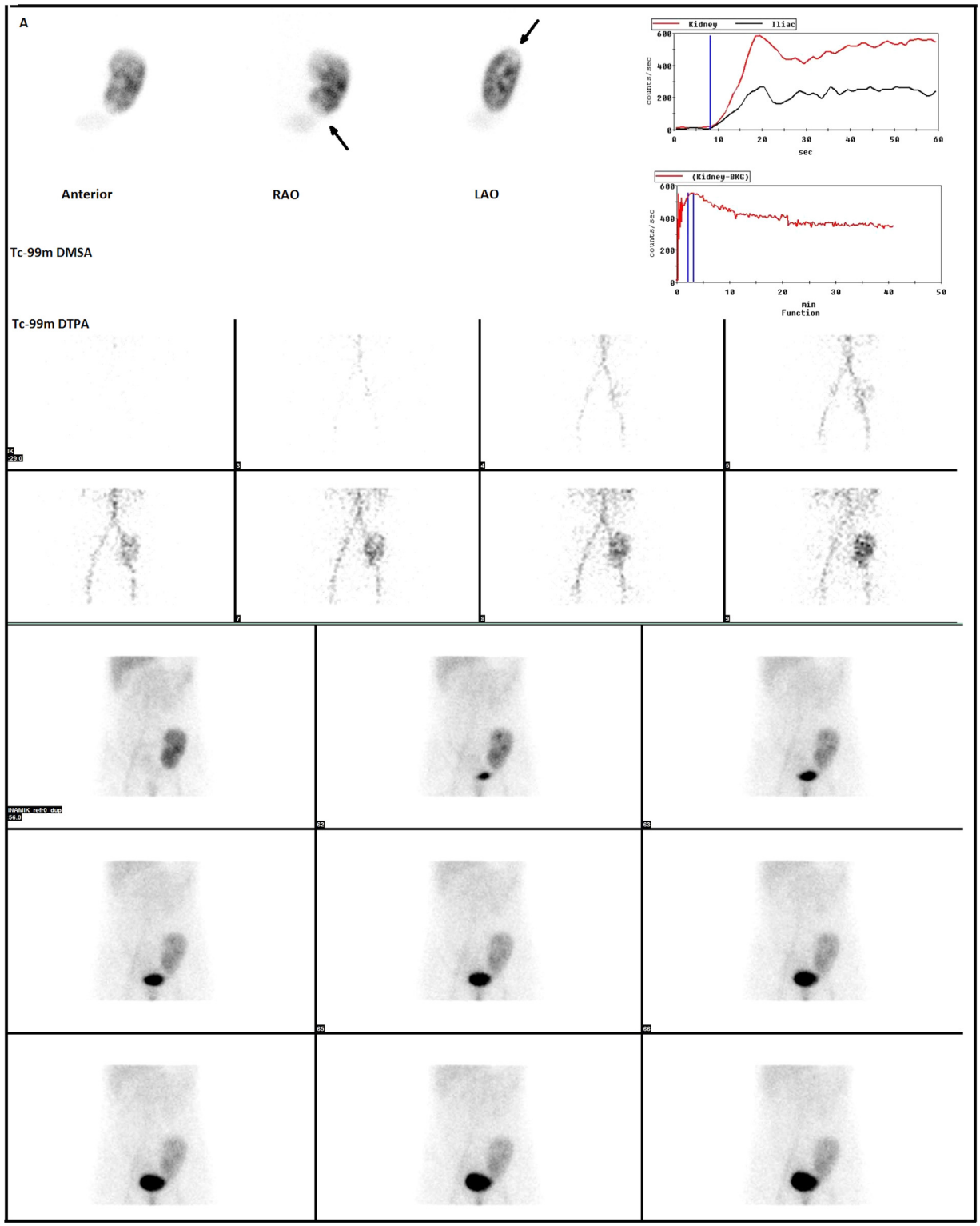

Figure 2 (A) Sixteen -year-old female patient had renal transplant from a living donor. She was admitted to hospital with dysuria and urge to urination after 3 months of transplantation. Urine analysis showed increased leukocytes and increased serum creatinine level (1.25 mg/dL). Color Doppler US was normal. Tc-99m DMSA scan was performed and revealed decreased uptake of Tc-99m DMSA at the upper and lower pole of the transplanted kidney (arrows). The BK virus load was increased on urine PCR and the biopsy confirmed BK virus nephropathy. A Tc-99m DTPA scan returned to normal after 6 months. (B) She was admitted to hospital with high creatinine level (4.17 mg/dL) at 14th month of follow-up and had both Tc-99m DTPA and Tc-99m MAG3 on two sequential days to rule out rejection. Both radionuclide renograms showed good perfusion. Tc-99m DTPA showed impaired glomerular function without peak activity, which can be compatible with ATN. However, Tc-99m MAG scintigraphy revealed heterogeneous radiotracer uptake and good extraction. Radiotracer excretion was slightly impaired with borderline R20/3 ratio. BK virus urinary PCR showed high viral load (488,000,000) and BK virus nephropathy was diagnosed on renal biopsy.

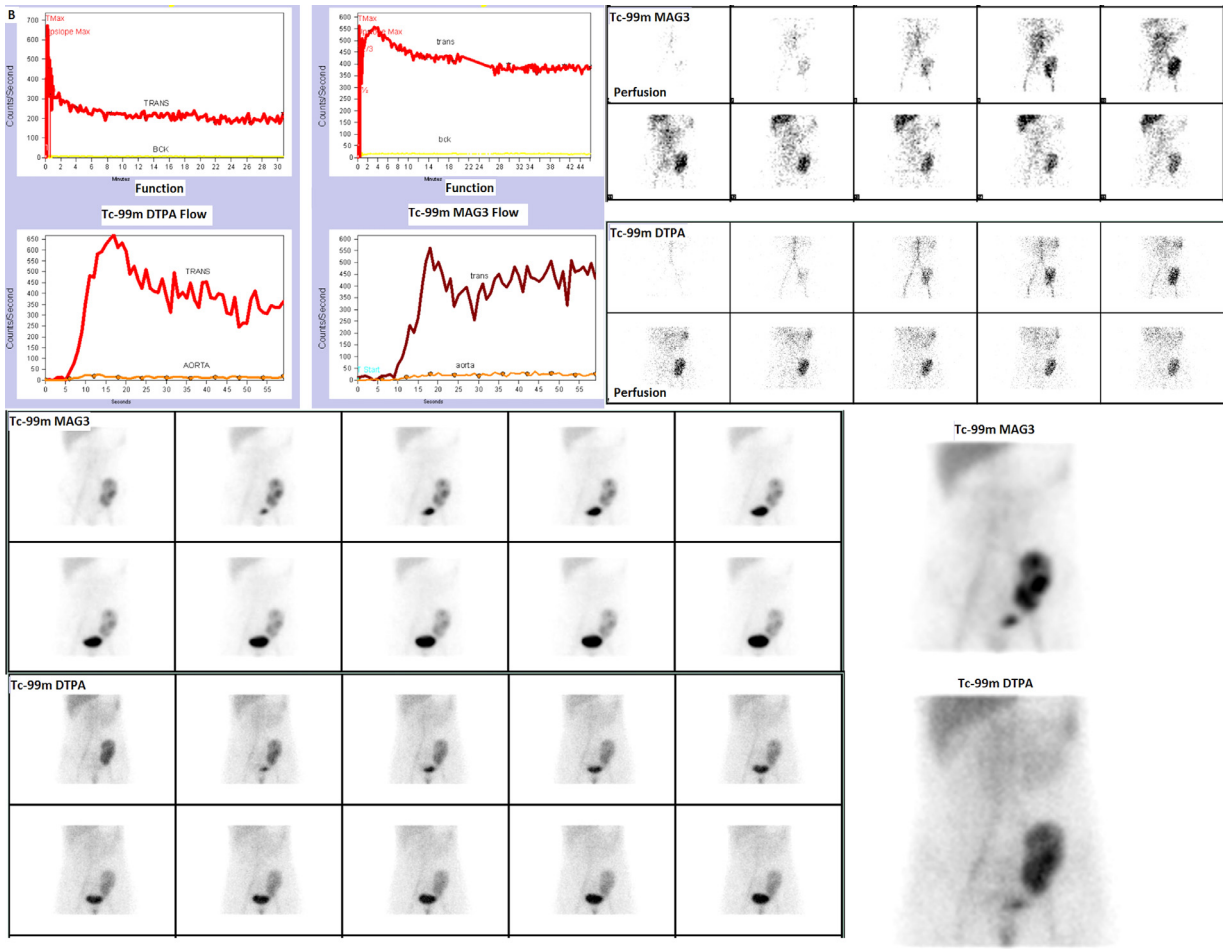

Figure 2 Continued.

function by accumulation index R20/3 in 146 scintigraphies using Tc-99m DTPA and showed that it can identify normal graft function, but it cannot differentiate ATN from acute rejection.[42] R20/3 was proposed to significantly predict the graft function at the end of first year.[24] Among the excretion–uptake indices, graft index (GI) (Table 3) was shown to increase as the graft function worsens.[31] GI had the sensitivity of 86.1% and specificity of 86.2% to identify DGF at 1st week after transplantation, and it can be used as a prognostic factor to predict transplant function at the end of first year.[19,40]

Russell *et al* showed that baseline ERPF values measured using single-injection, single plasma sample method with I-131-OIH or corrected ERPF values with Tc-99m-MAG3 had significant predictor power for 1-year graft survival in patients with cadaveric transplants.[32] In addition, they noted that Tmax and R20/3 values had also very good prognostic value. They concluded that single-sample ERPF measured in the immediate post-transplant period, whether from OIH clearance or Tc-99m MAG3 clearance, was a statistical predictor of graft survival for cadaveric transplants.[32]

DRS is sensitive to change in renal function; however, differentiation between types of rejection cannot be made clearly (Fig. 5). The patients should proceed to renal biopsy for the histopathological diagnosis and therapy management. Although renal US and color Doppler US is the first diagnostic choice for the graft evaluation, it is operator dependent and cannot reveal proper diagnosis on routine practice. DRS is not operator dependent; therefore, it still has the ability to diagnose worsening perfusion of renal allograft, even though the color Doppler US was reported to be normal or suspicious (Fig. 5).

Apart from quantitative analysis and time activity curve analysis, Adrakani *et al* performed texture analysis on Tc-99m DTPA scintigraphies on different time points, and showed that texture analysis parameters an 5 min had the highest diagnostic power.[45] The sensitivity and specificity of the multi-parameter texture analysis to differentiate rejection from non-rejection were 92.3% and 96.3%, respectively.[45] The authors also showed that multiparameter texture analysis were able to identify ATN from acute rejection with a sensitivity of 88% and specificity of 92.3%.[45] Although the results were promising, validation of the software should be performed by prospective studies other groups.

DRS was suggested for the indication of urinary obstruction and urinary leaks (Fig. 5).[13] Strictures of ureter can be seen as a late complication of surgery. Urinary leaks or urinomas when located close to either renal transplant of urinary bladder can be masked by the radioactivity of high concentration.[46] SPECT-CT was shown to be helpful for such

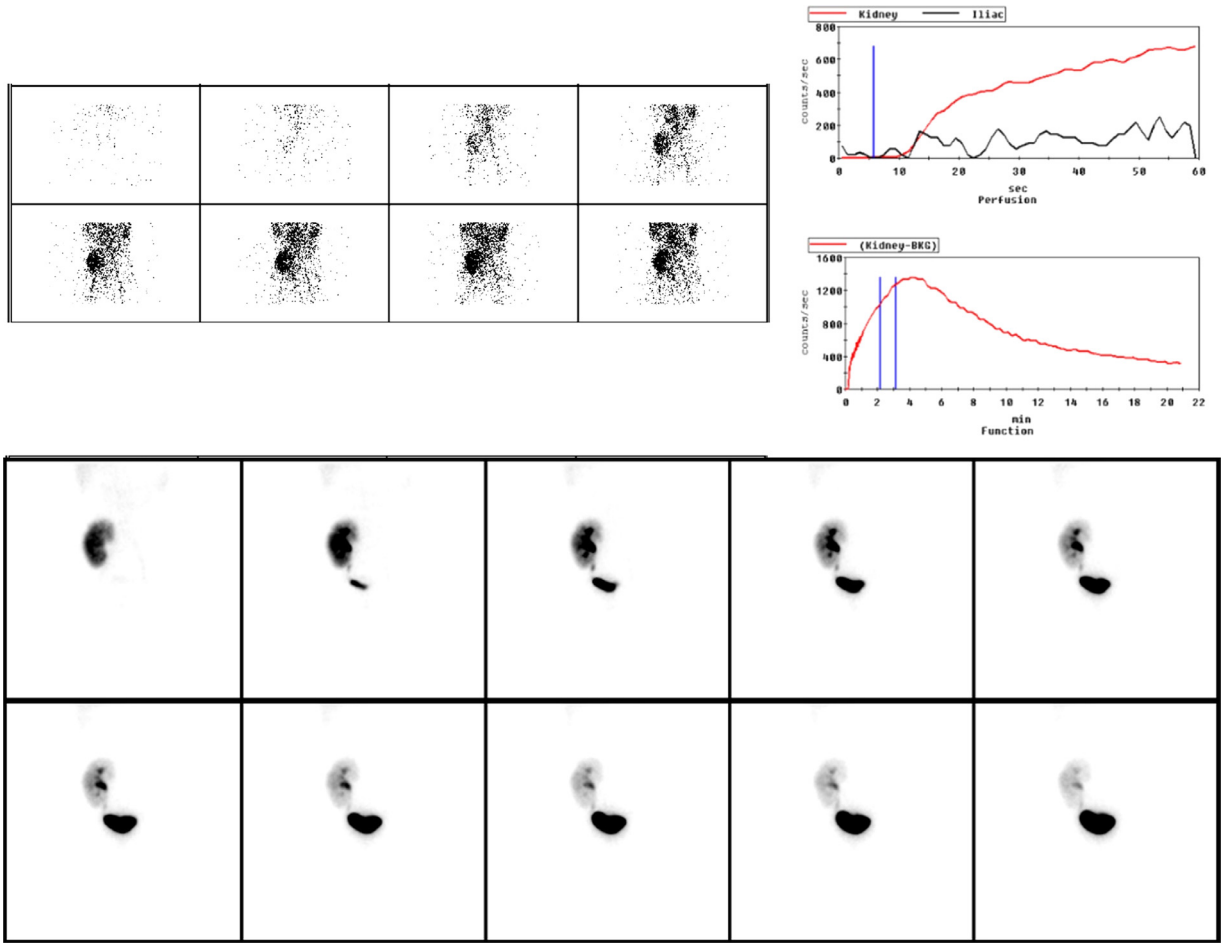

Figure 3 Thirteen-year-old female had renal transplant from a living relative. Baseline Tc-99m MAG3 study shows normal perfusion curve with first pass peak followed by a second peak showing early tubular extraction which was characteristic for the radiotracer. The function curve shows normal uptake and excretion.

conditions.[47] Ureter strictures or ureteral reflux are the complications seen in the first 6 months and DRS is sensitive on the diagnosis (Fig. 6). Examination of cinematic displays and TAC analysis can lead to the diagnosis most of the time. DRS is a powerful tool for the diagnosis of urinary leak especially with the use of SPECT-CT images.

DRS has high negative predictive value in renal transplant patients.[33,48] However, the procedure unfortunately fails to differentiate ATN from rejection.[33] Moreover, it has low diagnostic power in differentiating antibody related changes from T cell mediated rejection.[48]

b. Static Renal Scintigraphy

Tc-99m DMSA is currently used to detect renal scarring due to pyelonephritis. It binds to microproteins in plasma, and it is filtered through glomerulus. DMSA- microprotein complexes are taken up by receptor (megalin-cubulin) mediated endocytosis in proximal tubule cells.[49] The radiopharmaceutical is trapped in the cells, showing the cortical integrity of kidneys. However, it is not specific for infection. Scars, tumors, cysts etc. also do not take Tc-99m DMSA.

Renal allografts are always prone to infection starting with the early post-operative period. Variable infective pathogens are responsible from graft infection, starting with nosocomial and donor related infections in the early post-operative period. After 1 month of transplantation, latent infections or opportunistic infections are responsible. Apart from the cause, Tc-99m DMSA can be used to identify acute infection site and in the follow-up for renal scars (Fig. 1).[50] Renal scarring shown to be frequent in transplanted kidneys; therefore, it is advised to perform Tc-99m DMSA scan after 4-6 months of a confirmed pyelonephritis episode.[9,50]

Tc-99m DMSA's utility to differentiate between acute rejection and immunosuppressive drug toxicity was investigated in 24 patients and found not to be helpful for such purpose.[51] However, it has high sensitivity in the diagnosis of allograft infection, but has less specificity due to cyclosporin related micro-infarctions. Although Tc-99m DMSA is sensitive, the causes that are responsible from these defects are multifactorial; therefore, a baseline Tc-99m DMSA scan can be helpful in the patient follow-up.[50]

c. Cr-51 EDTA

Estimation of GFR is done using Cockcroft-Gault, Modification of Diet in Renal Disease , or Chronic Kidney Disease Epidemiology Collaboration formulas using

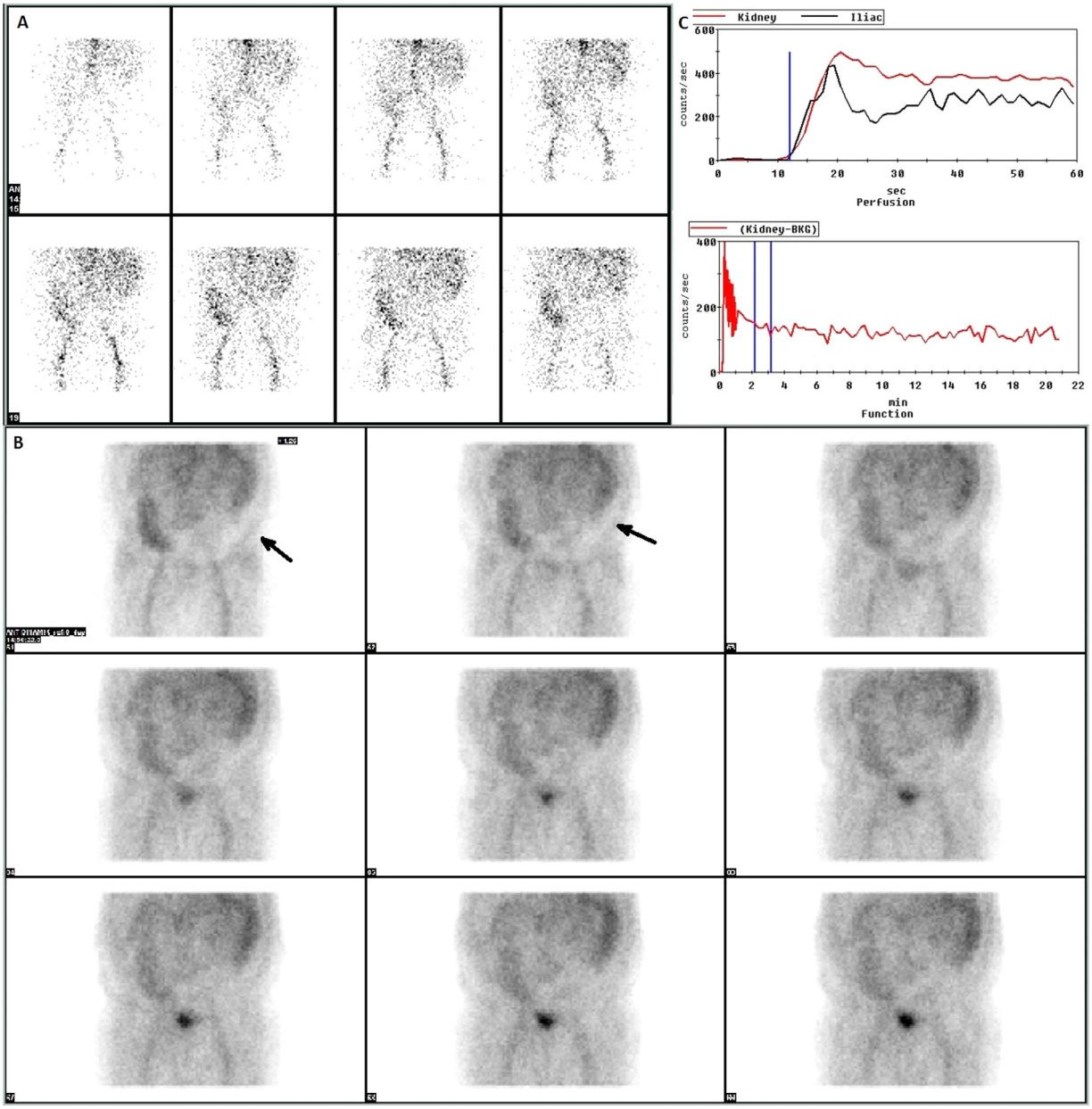

Figure 4 Fifty-four-year-old male patient had renal transplant from a deceased donor. On the fourth day of the transplantation the patient had nausea, vomiting and abdominal tenderness at the operation site. Abdominal US reported increased RI, intraabdominal collection and increased intestinal gas. The patient was admitted to Tc-99m DTPA DRS for the suspicion of urinoma (creatinine: 7.08 mg/dL). The renal transplant had decreased perfusion (A) and glomerular function of the transplant (B). Perfusion phase and function phase TAC's (C) were also consistent with the visual findings. Renal biopsy was done on the ninth day and revealed tubular microangiopathy and severe tubular degeneration. He had persistent fever, dyspnea in April 2020 and hospitalized when his COVID PCR was positive with the diagnosis of COVID'19 pneumonia. The pneumonia was treated, and the patient was transferred to internal medicine service from intensive care unit. On the follow-up he had fever and abdominal pain once again. His diagnose was CMV infection, PCR revealed increased viral load. On the seventh month of transplantation he was deceased due to CMV septicemia.

serum creatinine levels. However, all these formulas have systemic bias in estimating GFR. GFR measurement using Cr-51 EDTA remains as the gold standard.[52] RDS using Tc-99m DTPA can be an alternative for measurement of GFR; however, the protein binding fraction changes among the commercial kits available, lacking consistency. Recently Cr-51 EDTA was used in combination with Tc-99m DMSA in living donors before transplantation to estimate both single kidney GFR in donor and transplant.[53] However, no association was present between pre-operative single kidney GFR and transplant function at the end of first year.[53]

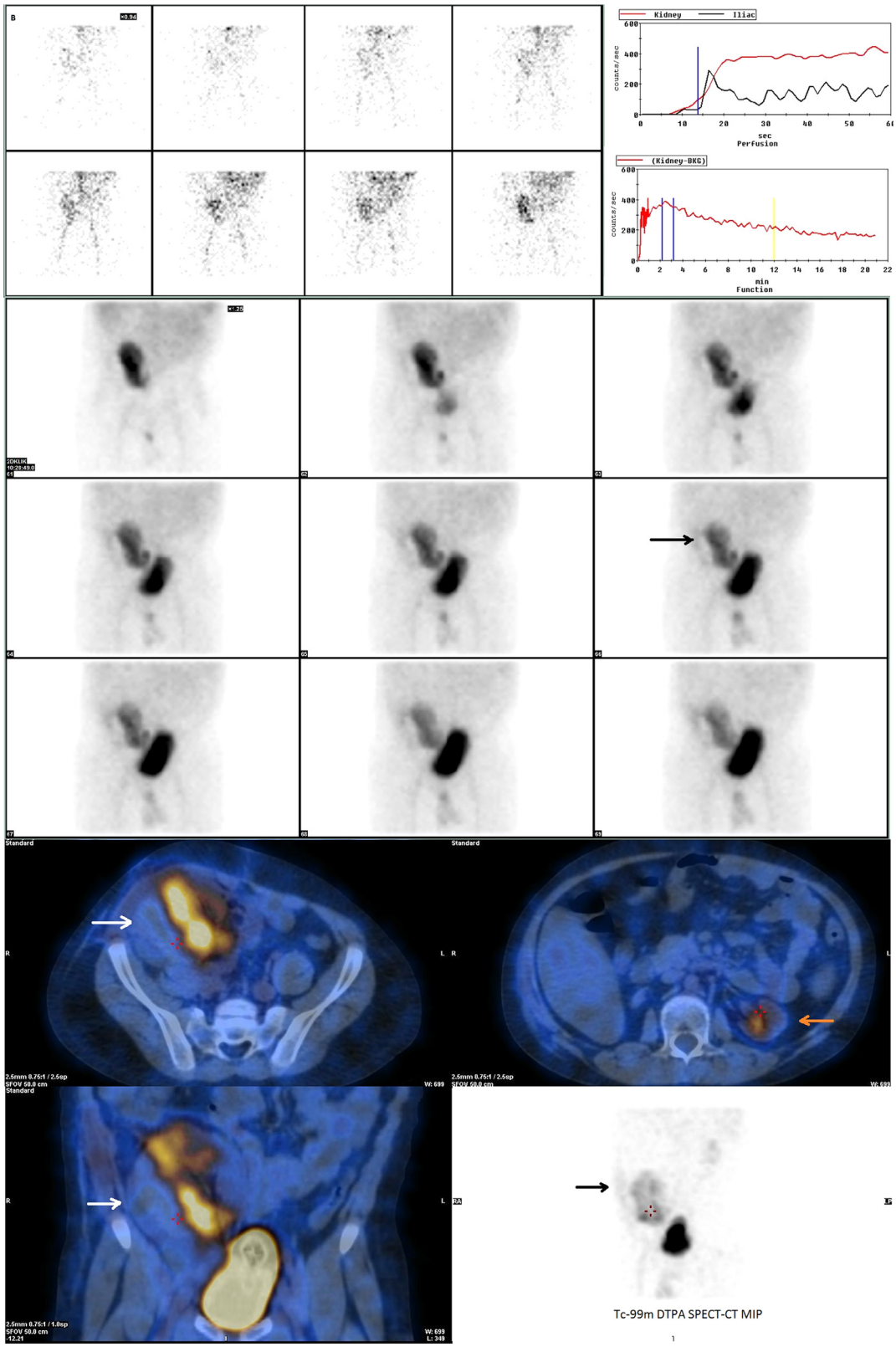

Figure 5 (A) Ten-year-old male patient had renal transplant from a living donor and had increased serum creatinine level (0.98 mg/dL). The US revealed a perirenal collection and slightly elevated RI. Tc-99m DTPA DRS revealed nearly normal perfusion visually with grade 2 perfusion curve semi-quantitatively. The 2 min dynamic images, SPECT-CT images and MIP image revealed peri-renal urine collection (arrows). SPECT-CT images also revealed ureteral reflux to the left native kidney (orange arrow) (B) Same patient had increased creatinine level (1.64 mg/dL) after 1 year. The renal US revealed increased RI on the lower pole of the kidney and concluded suspicion of rejection. Tc-99m DTPA DRS revealed decreased perfusion on both visual analysis and TAC, but nearly normal glomerular function. The renal biopsy was carried out revealing borderline T-cell mediated rejection. (C) On the 15th month after renal transplantation of the patient, increased serum creatinine levels (1.76 mg/dL) were detected at the 14th month. Renal color Doppler US was reported normal. The Tc-99m DTPA DRS was performed. The renal transplant had decreased perfusion, more prominent when compared to the previous DRS on visual analysis and perfusion curve. The glomerular function was slightly diminished with increased background radioactivity. Transplant biopsy revealed acute T cell mediated rejection.

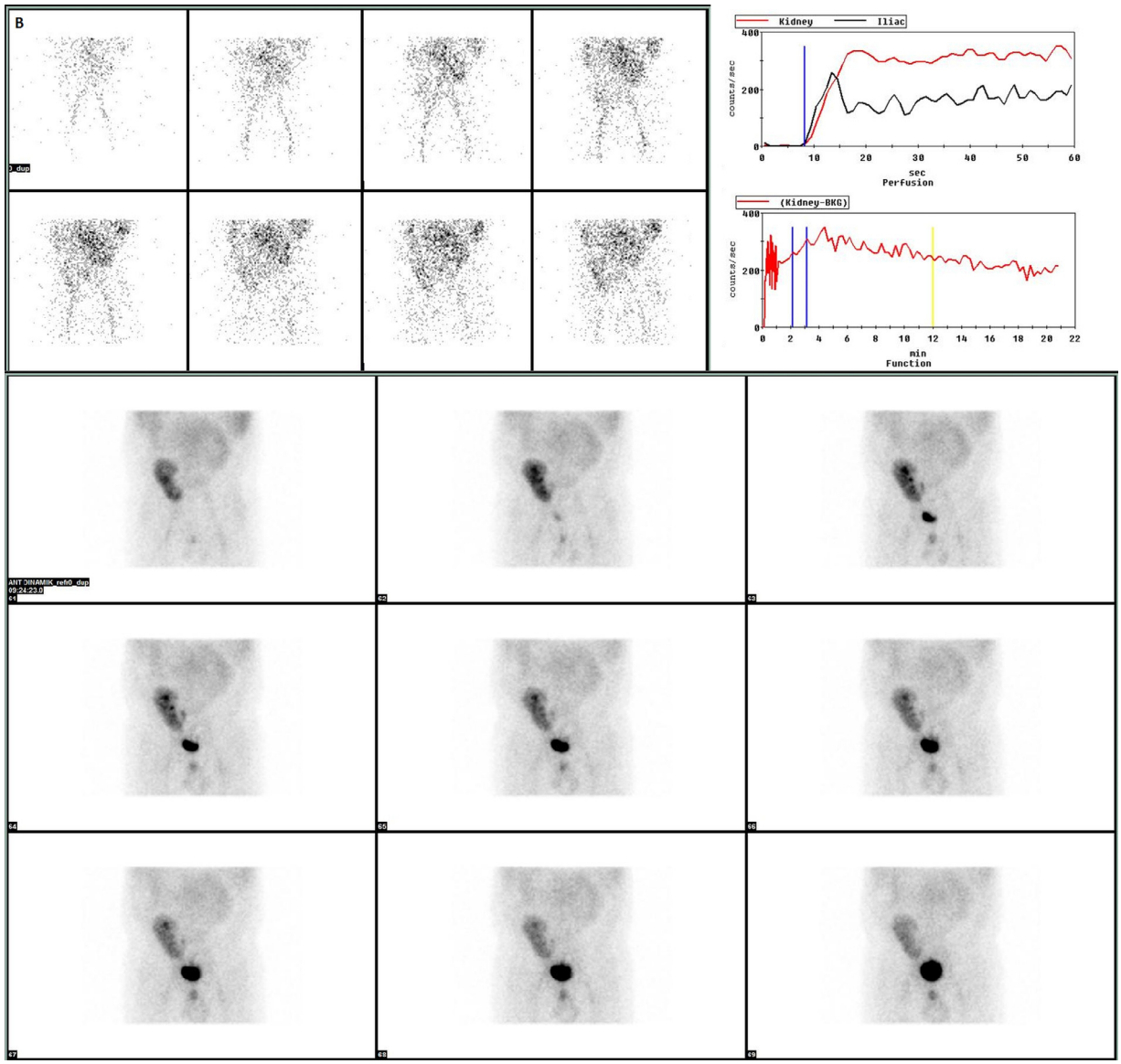

Figure 5 Continued.

Imaging Rejection

Sulfur Colloid Scintigraphy

Use of Tc-99m sulfur colloid was proposed in early 70s, and imaging principle is the presence of multiple fibrin thrombus in rejection. The radiocolloid, normally taken up by reticuloendothelial system, is trapped in renal microvasculature, leading to the visualization of the graft if the patient had rejection, cardiac failure or sepsis.[54,55] In a study where 54 transplant patients' sulfur colloid scintigraphies were compared to both Tc-99m DTPA DRS and the results of renal biopsies, the authors concluded that it might be a good predictor in differentiating acute or chronic rejection from other causes of transplant dysfunction.[56] However, because it focuses on the result and not the cause, the use of Tc-99m sulfur colloid did not find worldwide application in renal transplant imaging.

Radiolabelled Leucocyte Scintigraphy

The first use of In-111 labelled white blood cells was done by Frick *et al* in renal transplant patients to diagnose rejection.[57] Lopes de Sauza *et al* used Tc-99m mononuclear leucocyte imaging in 100 transplant patients and compared the uptake with renal transplant biopsies.[58] The authors proposed that radiolabeled leucocytes had the ability to differentiate rejection from ATN, and therefore, it can be used in the early diagnosis of rejection with the sensitivity of 81% and positive predictive value of 100%.[58]

Grabner *et al* labelled T-cells with F-18 FDG and imaged renal allograft rejection in rats.[59] They concluded that imaging with FDG labelled T lymphocytes resulted in less radiation burden when compared to conventional F-18 FDG imaging, and the excretion of radiopharmaceutical was far less allowing the better visualization of renal transplant.[59]

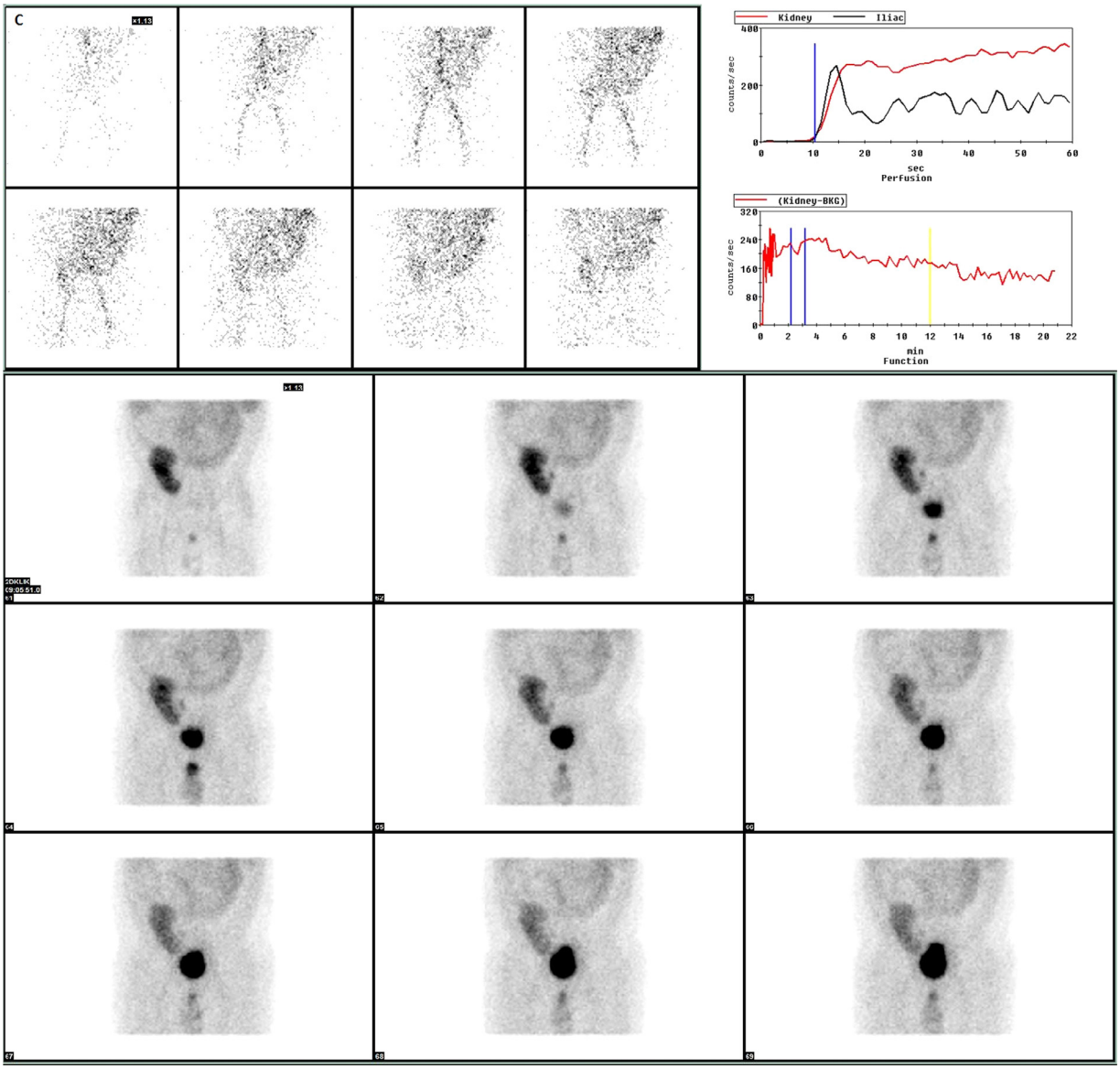

Figure 5 Continued.

FDG labelled leucocytes are used in humans for identification of infection in pancreatic collections, but use in human renal transplant is lacking in literature.[60]

F-18 FDG PET-CT

It has shown that activated leucocytes are in the acute rejection of renal allografts. The activated white blood cells require energy and therefore increase GLUT1 expression. This is the main reason that F-18 FDG is taken up in the infection site. F-18 FDG is filtrated through glomeruli and taken up by the tubular cells. This uptake does not depend on renal function. Jadoul *et al* reported that there was no correlation between F-18 FDG uptake in renal allografts and glomerular filtration rate values, and chronic renal impairment status had no impact on F-18 FDG uptake.[61] In a study, 20 renal failure patients had similar F-18 FDG uptake when compared to healthy volunteers.[62] These studies both showed that if F-18 FDG uptake increases, it is due to inflammation in renal transplant patients. In an observational cohort study, Lovinfosse *et al* correlated FDG uptake with the patients' allograph biopsy results.[63] They showed that F-18 FDG uptake had correlation with both the severity of leucocyte infiltrate and inflammation; moreover, with the mean F-18 FDG uptake threshold of 1.6 they successfully identified rejection patients with negative predictive value of 100%.[63] In another observational study of 92 patients, mean standard uptake ratios were significantly higher in acute rejection patients; however, F-18 FDG PET did not identify borderline category of Banff classification from normal histopathological findings.[64] Interobserver variability of standardized uptake values of F-18 FDG were high and according to Jadoul *et al* it can be used in routine in the identification of acute rejection renal transplant patients.[65]

Ga-68 Pentixafor

C-X-C chemokine receptor 4 was involved on leucocyte trafficking in renal transplant infections and therefore targeted by Ga-68 pentixafor.[66] The radiopharmaceutical successfully

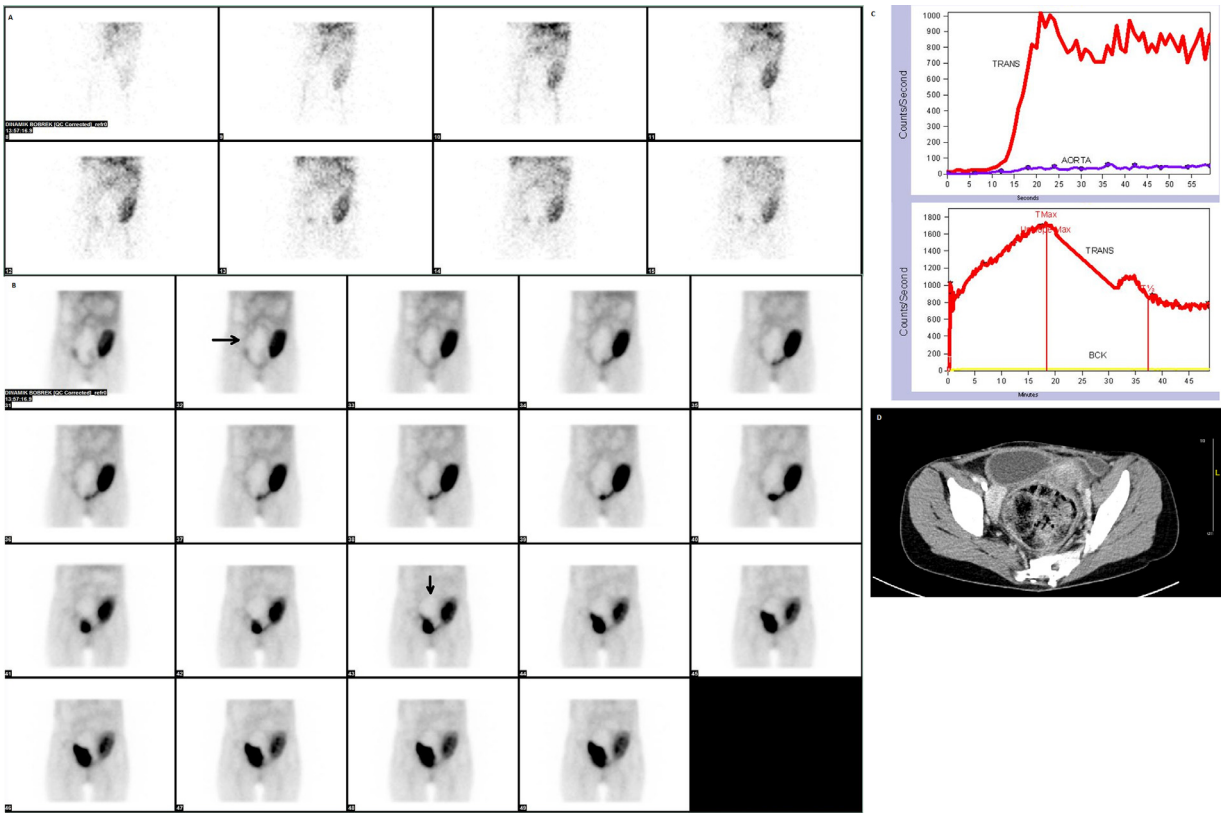

Figure 6 Twenty-year-old female patient, with previously operated cloaca abnormality and anal atresia, had renal transplant from a living donor and had fever after 1 week. Urine analysis revealed increased leukocytes, abdominal US reported pelvicalyceal dilatation. The patient had prolonged constipation. Tc-99m DTPA DRS revealed normal perfusion of renal transplant (A). Two-minute static images revealed a large hypoactive area (arrows) medial to renal bladder and a filling defect at the upper border of the late 2 minute dynamic images (B). TAC showed vesicoureteral reflux after 30 minutes (C). The large hypoactive area was correlated with the pre-operative abdominal CT images and dilated sigmoid colon was responsible from bladder indentation (D).

diagnosed both allograft infection and lower urinary tract infection in 13 patients, which was confirmed histopathologically. However, its use in renal transplant rejection has not been studied yet.

Future Prospects

Of the new PET radiopharmaceuticals that are introduced for the assessment of renal function, Ga-68 EDTA was tested on six healthy subjects and reported to be useful for the quantification measurement of GFR.[67] Hofman *et al* showed a good agreement between GFR measurements of Ga-68 EDTA and Cr-51 EDTA in 31 patients.[68] The other radiotracer freely filtrated at glomerulus was 2-deoxy-2 [F-18]fluorosorbitol (F-18 FDS) which resembles inositol. F-18 FDS was used in two healthy volunteers and shown to be rapidly cleared from circulatory system and excreted in the urine.[69] Dynamic renal imaging of native kidneys using PET camera has the limitation of narrow field of view. Imaging both native kidneys and bladder is not possible; however, this would not be a problem for transplanted kidneys. High quality 3D images and quantitative measurement of GFR might provide meticulous follow-up of renal transplant patients. Another radiotracer that resembles I-131 Orthoidodohippurate is Re(CO)3 (2-[18F]fluoroethyl)iminodiacetic acid (F-18 FEDA).[70] F-18 FEDA had high protein binding and a rapid renal clearance, and radiopharmaceutical showed high in vivo and in vitro stability on animal studies.[70]

References

1. Nagy J: A note on the early history of renal transplantation: Emerich (Imre) Ullmann. Am J Nephrol 19:346-349, 1999
2. Starzl TE, Marchioro TL, Waddell WR: The reversal of rejection in human renal homografts with subsequent development of homograft tolerance. Surg Gynecol Obstet 117:385-395, 1963
3. Loken MK SEV, Vernier RL, Kelly W: Radioisotope renogram in kidney transplants1. J Nucl Med 5:807-810, 1964
4. Blaufox MD, Aurell M, Bubeck B, et al: Report of the radionuclides in nephrourology committee on renal clearance. J Nucl Med 37:1883-1890, 1996
5. Fleming JS, Zivanovic MA, Blake GM, et al: Guidelines for the measurement of glomerular filtration rate using plasma sampling. Nucl Med Commun 25:759-769, 2004
6. Hilson AJ, Maisey MN, Brown CB, et al: Dynamic renal transplant imaging with Tc-99m DTPA (Sn) supplemented by a transplant perfusion index in the management of renal transplants. J Nucl Med 19:994-1000, 1978
7. Staab EV, Kelly WD, Loken MK: Prognostic value of radioisotope renograms in kidney transplantation. J Nucl Med 10:133-135, 1969

8. Fritzberg AR, Kasina S, Eshima D, et al: Synthesis and biological evaluation of technetium-99m MAG3 as a hippuran replacement. J Nucl Med 27:111-116, 1986
9. Damasio MB, Ording Muller LS, Piaggio G, et al: Imaging in pediatric renal transplantation. Pediatr Transplant 21, 2017
10. Russell CD, Dubovsky EV: Reproducibility of single-sample clearance of 99mTc-mercaptoacetyltriglycine and 131I-orthoiodohippurate. J Nucl Med 40:1122-1124, 1999
11. Bubeck B: Renal clearance determination with one blood sample: improved accuracy and universal applicability by a new calculation principle. Semin Nucl Med 23:73-86, 1993
12. Kabasakal L, Yapar AF, Ozker K, et al: Simplified technetium-99m-EC clearance in adults from a single plasma sample. J Nucl Med 38:1784-1786, 1997
13. Breda (Chair) KB A, Figueiredo A, Lledó García E, et al: Guidelines Associates: EAU guidelines on renal transplantation. Urology EAo: 375-398, 2017
14. Jeong HJ: Diagnosis of renal transplant rejection: Banff classification and beyond. Kidney Res Clin Pract 39:17-31, 2020
15. Loupy A, Haas M, Roufosse C, et al: The banff 2019 kidney meeting report (I): updates on and clarification of criteria for T cell- and antibody-mediated rejection. Am J Transplant 20:2318-2331, 2020
16. Daly PJ, Power RE, Healy DA, et al: Delayed graft function: a dilemma in renal transplantation. BJU Int 96:498-501, 2005
17. Erbas B: Peri- and postsurgical evaluations of renal transplant. Semin Nucl Med 47:647-659, 2017
18. Siedlecki A, Irish W, Brennan DC: Delayed graft function in the kidney transplant. Am J Transplant 11:2279-2296, 2011
19. Zens TJ, Danobeitia JS, Leverson G, et al: The impact of kidney donor profile index on delayed graft function and transplant outcomes: A single-center analysis. Clin Transplant 32:e13190, 2018
20. Halloran PF, Hunsicker LG: Delayed graft function: State of the art, November 10-11, 2000. Summit meeting, Scottsdale, Arizona, USA. Am J Transplant 1:115-120, 2001
21. Wu WK, Famure O, Li Y, et al: Delayed graft function and the risk of acute rejection in the modern era of kidney transplantation. Kidney Int 88:851-858, 2015
22. Goldberg RJ, Weng FL, Kandula P: Acute and chronic allograft dysfunction in kidney transplant recipients. Med Clin North Am 100:487-503, 2016
23. Expert Panel on Urologic I, Taffel MT, Nikolaidis P, et al: ACR appropriateness criteria((R)) renal transplant dysfunction. J Am Coll Radiol 14: S272-S281, 2017
24. Yazici B, Oral A, Gokalp C, et al: Evaluation of renal transplant scintigraphy and resistance index performed within 2 days after transplantation in predicting long-term graft function. Clin Nucl Med 40:548-552, 2015
25. Aktas A, Aras M, Colak T, et al: Comparison of Tc-99m DTPA and Tc-99m MAG3 perfusion time-activity curves in patients with renal allograft dysfunction. Transplant Proc 38:449-453, 2006
26. Gupta SK, Lewis G, Rogers KM, et al: Quantitative (99m)Tc DTPA renal transplant scintigraphic parameters: Assessment of interobserver agreement and correlation with graft pathologies. Am J Nucl Med Mol Imaging 4:213-224, 2014
27. Kirchner PT, Goldman MH, Leapman SB, et al: Clinical application of the kidney to aortic blood flow index (K/A ratio). Contrib Nephrol 11:120-126, 1978
28. Jackson SA, Ehrlich L, Martin RH: The renal washout parameter as an indicator of transplant rejection. Eur J Nucl Med 12:86-90, 1986
29. Koizumi K, Uchiyama G, Araki T, et al: [Tc-99m DTPA scintigraphic findings in patients with postoperative complications of renal transplantation]. Rinsho Hoshasen 34:1423-1432, 1989
30. El-Maghraby TA, Boom H, Camps JA, et al: Delayed graft function is characterized by reduced functional mass measured by (99m)Technetium-mercaptoacetyltriglycine renography. Transplantation 74:203-208, 2002
31. Yazici B: Practical method for calculation of graft index in renal transplant scintigraphy: A technical note. Clin Nucl Med 44:32-37, 2019
32. Russell CD, Yang H, Gaston RS, et al: Prediction of renal transplant survival from early postoperative radioisotope studies. J Nucl Med 41:1332-1336, 2000
33. Lee SF, Lichtenstein M, Hughes P, et al: Utility of MAG3 scintigraphy with the use of a 2 min uptake parameter in the assessment of postsurgical renal transplant complications. Nucl Med Commun 39:921-927, 2018
34. Li Y, Russell CD, Palmer-Lawrence J, et al: Quantitation of renal parenchymal retention of technetium-99m-MAG3 in renal transplants. J Nucl Med 35:846-850, 1994
35. Shikano N, Kanai Y, Kawai K, et al: Transport of 99mTc-MAG3 via rat renal organic anion transporter 1. J Nucl Med 45:80-85, 2004
36. Dubovsky EV, Russell CD, Bischof-Delaloye A, et al: Report of the radionuclides in nephrourology committee for evaluation of transplanted kidney (review of techniques). Semin Nucl Med 29:175-188, 1999
37. Ayaz S AA, Moray G: TPA and MAG3 scintigraphy in acute renal allograft dysfunction: comparison of diagnostic values. [J Clin Anal Med 8:14-18, 2017
38. el Maghraby TA, van Eck-Smit BL, de Fijter JW, et al: Quantitative scintigraphic parameters for the assessment of renal transplant patients. Eur J Radiol 28:256-269, 1998
39. Ngai S, Demetriades T: Prediction of long-term renal transplant allograft function from day 3 post-transplant Tc-99m MAG3 scintigraphy. Clin Nucl Med 33:102-105, 2008
40. Yazici B, Oral A, Gokalp C, et al: A new quantitative index for baseline renal transplant scintigraphy with 99mTc-DTPA in evaluation of delayed graft function and Prediction of 1-year graft function. Clin Nucl Med 41:182-188, 2016
41. Guignard R, Mourad G, Mariano-Goulart D: Utility of postsurgical renal scintigraphy to predict one-year outcome of renal transplants in patients with delayed graft function. Nucl Med Commun 32:314-319, 2011
42. Yazici B, Yazici A, Oral A, et al: 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 38:931-935, 2013
43. Benjamens S, Pol RA, Berger SP, et al: Limited clinical value of two consecutive post-transplant renal scintigraphy procedures. Eur Radiol 30:452-460, 2020
44. Benjamens S, Pol RA, de Geus-Oei LF, et al: Can transplant renal scintigraphy predict the duration of delayed graft function? A dual center retrospective study. PLoS One 13:e0193791, 2018
45. Ardakani AA, Hekmat S, Abolghasemi J, et al: Scintigraphic texture analysis for assessment of renal allograft function. Pol J Radiol 83:e1-e10, 2018
46. Gunatunga I, Facey P, Bartley L, et al: Perinephric urinoma secondary to perforated UPJ obstruction diagnosed using Tc-99m mercaptoacetyltriglycine (MAG3) SPECT/CT. Clin Nucl Med 32:317-319, 2007
47. Yazici B, Oral A, Akgun A: Contribution of SPECT/CT to evaluate urinary leakage suspicion in renal transplant patients. Clin Nucl Med 43: e378-e380, 2018
48. Heaf JG, Iversen J: Uses and limitations of renal scintigraphy in renal transplantation monitoring. Eur J Nucl Med 27:871-879, 2000
49. Weyer K, Nielsen R, Petersen SV, et al: Renal uptake of 99mTc-dimercaptosuccinic acid is dependent on normal proximal tubule receptor-mediated endocytosis. J Nucl Med 54:159-165, 2013
50. Hutchinson C, Beckett M, Kiratli P, et al: The significance of a defect on DMSA scan in children with renal transplants. Pediatr Transplant 7:441-445, 2003
51. Garin E, Devillers A, Rivalan J, et al: Contribution of 99Tcm-DMSA scintigraphy to aetiological diagnosis in renal transplant recipients with impaired renal function. Nucl Med Commun 21:77-81, 2000
52. Gaspari F, Ferrari S, Stucchi N, et al: Performance of different prediction equations for estimating renal function in kidney transplantation. Am J Transplant 4:1826-1835, 2004
53. Heitz M, Jouve T, Roustit M, et al: Predonation single kidney glomerular filtration rate in living kidney transplantation to predict graft function and donor functional gain. Transplant Proc 52:712-721, 2020
54. Frick MP, Loken MK, Goldberg ME, et al: Use of 99mTc-sulfur colloid in evaluation of renal transplant complications. J Nucl Med 17:181-183, 1976
55. Solaric-George EA, Fletcher JW, Newton WT, et al: Renal accumulation of 99mTc sulfur colloid in transplant rejection. Radiology 111:465-466, 1974

56. Einollahi B, Bakhtiari P, Simforoosh N, et al: Renal allograft accumulation of technetium-99m sulfur colloid as a predictor of graft rejection. Transplant Proc 37:2973-2975, 2005
57. Frick MP, Henke CE, Forstrom LA, et al: Use of 111In-labeled leukocytes in evaluation of renal transplant rejection: A preliminary report. Clin Nucl Med 4:24-25, 1979
58. Lopes de Souza SA, Barbosa da Fonseca LM, Torres Goncalves R, et al: Diagnosis of renal allograft rejection and acute tubular necrosis by 99mTc-mononuclear leukocyte imaging. Transplant Proc 36:2997-3001, 2004
59. Grabner A, Kentrup D, Edemir B, et al: PET with 18F-FDG-labeled T lymphocytes for diagnosis of acute rat renal allograft rejection. J Nucl Med 54:1147-1153, 2013
60. Bhattacharya A, Kochhar R, Sharma S, et al: PET/CT with 18F-FDG-labeled autologous leukocytes for the diagnosis of infected fluid collections in acute pancreatitis. J Nucl Med 55:1267-1272, 2014
61. Jadoul A, Lovinfosse P, Weekers L, et al: The uptake of 18F-FDG by renal allograft in Kidney kransplant recipients is not influenced by renal function. Clin Nucl Med 41:683-687, 2016
62. Minamimoto R, Takahashi N, Inoue T: FDG-PET of patients with suspected renal failure: Standardized uptake values in normal tissues. Ann Nucl Med 21:217-222, 2007
63. Lovinfosse P, Weekers L, Bonvoisin C, et al: Fluorodeoxyglucose F(18) positron emission tomography coupled with computed tomography in suspected acute renal allograft rejection. Am J Transplant 16:310-316, 2016
64. Hanssen O, Weekers L, Lovinfosse P, et al: Diagnostic yield of (18) F-FDG PET/CT imaging and urinary CXCL9/creatinine levels in kidney allograft subclinical rejection. Am J Transplant 20:1402-1409, 2020
65. Jadoul A, Lovinfosse P, Bouquegneau A, et al: Observer variability in the assessment of renal (18)F-FDG uptake in kidney transplant recipients. Sci Rep 10:4617, 2020
66. Derlin T, Gueler F, Brasen JH, et al: Integrating MRI and chemokine receptor CXCR4-targeted PET for detection of leukocyte infiltration in complicated urinary tract infections after kidney transplantation. J Nucl Med 58:1831-1837, 2017
67. Yamashita M, Inaba T, Kawase Y, et al: Quantitative measurement of renal function using Ga-68-EDTA. Tohoku J Exp Med 155:207-208, 1988
68. Hofman M, Binns D, Johnston V, et al: 68Ga-EDTA PET/CT imaging and plasma clearance for glomerular filtration rate quantification: Comparison to conventional 51Cr-EDTA. J Nucl Med 56:405-409, 2015
69. Werner RA, Ordonez AA, Sanchez-Bautista J, et al: Novel functional renal PET imaging with 18F-FDS in human subjects. Clin Nucl Med 44:410-411, 2019
70. Lipowska M, Jarkas N, Voll RJ, et al: Re(CO)3([(18)F]FEDA), a novel (18)F PET renal tracer: Radiosynthesis and preclinical evaluation. Nucl Med Biol 58:42-50, 2018