Asia-Pacific Journal of Science and Technology: Volume: 27. Issue: 06. Article ID.: APST-27-06-11. Research Article

APST

Asia-Pacific Journal of Science and Technology

https://www.tci-thaijo.org/index.php/APST/index

Published by the Research and Technology Transfer Affairs Division,
Khon Kaen University, Thailand

Comparative evaluation of Tc-99m DTPA and Tc-99m MAG3 post-transplant renal scintigraphy for predicting one-year renal function in kidney transplant recipients

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Received 30 September 2021
Revised 12 October 2021
Accepted 13 October 2021

Abstract

This study aimed to compare renal scintigraphy (RS) using Tc-99m DTPA and Tc-99m MAG3 for predicting suboptimal renal function 1-year after kidney transplantation (KT) and correlation with renal function. This retrospective study included patients who underwent Tc-99m DTPA and Tc-99m MAG3 RS within 30 days after KT. Patients with serum creatinine at 1-year of ≤1.5 mg/dL and >1.5 mg/dL were classified as having good and suboptimal renal function, respectively. Area under receiver operating characteristic curve (AUC_{ROC}) was used to determine predictiveness of RS parameters in predicting suboptimal renal function. Spearman's correlation was used to determine correlation between RS parameters and estimated glomerular filtration rate (eGFR). Of 227 patients, mean age was 42±10.5 years, 61.2% were males, 94.3% underwent deceased-donor KT. 56 patients (24.7%) had suboptimal 1-year renal function. The highest AUC_{ROC} is 0.71 for effective renal plasma flow rate from Tc-99m MAG3 RS but no significant differences in AUC_{ROC} between parameters from Tc-99m DTPA RS vs. Tc-99m MAG3 RS were found. Three parameters including time to peak, 20-min to peak ratio, and 20-min to 3-min, when obtained from Tc-99m MAG3 RS, had significant negative correlation with eGFR at 1-year (ρ: -0.18, -0.25, and -0.24, respectively) while those obtained from Tc-99m DTPA RS had no correlation.
Tc-99m DTPA and Tc-99m MAG3 RS had no significant difference in predicting 1-year suboptimal post-KT renal function. However, time to peak, 20-min to peak ratio, 20-min to 3-min ratio were better correlated with eGFR when obtained from Tc-99m MAG3 RS.

Keywords: Graft function, Graft outcome, Kidney transplantation, Radionuclide imaging, Renal scintigraphy

1. Introduction

Chronic kidney disease is a worldwide public health problem with prevalence ranging from 11 to 13% [1]. Patients with end-stage renal disease (ESRD) need either dialysis or kidney transplantation (KT) to prolong their survival [2]. Despite improvement of transplantation techniques and the use of immunosuppressive medication, acute and chronic graft rejection still occur and are detrimental to graft function and patient outcome, with graft failure occurring in approximately 15% of patients within 5 years after transplantation [3]. Various clinical factors such as delayed graft function, acute rejection, and type of donor, among others are determinants of the outcome of KT [4–6]. Serum creatinine at 1-year post-KT has also been used as an intermediary outcome measure with patients whose serum creatinine at 1-year higher than 1.5 mg/dL being more likely to have reduced graft survival rate at 5-years [7]. Nuclear medicine renal scintigraphy (RS) has long been used for evaluation of perfusion and function of renal graft post-transplantation. It is able to detect acute complications such as acute graft rejection and ischemic nephropathy [8–10] and can also predict long-term graft function [11]. The common radiopharmaceuticals for RS such as Tc-99m DTPA and Tc-99m MAG3 have been used in different studies, but

there have been few studies that directly compared Tc-99m DTPA RS and Tc-99m MAG3 RS for predicting renal function outcome after KT. Therefore, the objective of this study is to compare Tc-99m DTPA RS and Tc-99m MAG3 RS in terms of their predictiveness of renal function outcome as estimated by serum creatinine 1-year after KT.

2. Materials and methods

2.1 Patients

Adult ESRD patients underwent either living- or deceased-donor KT at our center. After KT, all patients received immunosuppression induction therapy with 1,000 mg of methylprednisolone. Basiliximab or thymoglobulin was also given to induce immunosuppression in selected cases depending on their HLA mismatch and panel reactive antibody. Tacrolimus was given as a maintenance drug with the therapeutic dose range of 5-8 ng/mL during the first 4 weeks, 5 ng/mL during the 5^{th} to 12^{th} week, and 3-5 ng/mL after the 12^{th} week. Additionally, either mycophenolate mofetil or mycophenolic acid was also included in the maintenance regimen. All participants were monitored serially for renal function after KT including blood urea nitrogen, serum creatinine, and urine output. The serum creatinine was used to determine the estimated glomerular filtration rate (eGFR) according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [12]. After discharge, patients were closely monitored with follow-up visits monthly during the first few months to assess their serum creatinine and tacrolimus levels. Follow-up interval was increased to every few months after the renal function and tacrolimus levels were stable. For this study, patients who were lost to follow-up before 1-year after KT were excluded. At 1-year after KT, patients with serum creatinine of $\leq$ 1.5 mg/dL were considered to have good renal function, and those with values > 1.5 mg/dL were considered to have suboptimal renal function.

2.2 Renal scintigraphy

During the postoperative period, all patients have received RS with Tc-99m DTPA and Tc-99m MAG3, successively. Only patients who received RS within 30 days after KT were included. In performing RS, a routine standard institutional protocol was used for all patients. First, an indwelling IV catheter attached to a three-way stopcock was inserted to the cubital vein before beginning of the examination. The first RS was done with 37 megabecquerels (MBq) of Tc-99m DTPA. The second RS was done with 185 MBq of Tc-99m MAG3 immediately after completion of the first RS. Image acquisition was done with the patient in supine position under a Discovery NM/CT 670 SPECT/CT system (GE Healthcare, IL, USA) equipped with a low-energy all-purpose collimator. Dynamic imaging using list mode acquisition was started simultaneously with bolus injection of the radiotracer with imaging matrix of 1,024 x 1,024 x 16, photopeak of 140 keV, and energy window of ±15%. Images were acquired in two phases: the perfusion phase at 1 sec/frame during the first min and the function phase at 20 sec/frame for the remaining 20 min. Radioactivity in the syringe was measured before and after injection by placing the syringe under a gamma camera at a distance of 30 cm for a duration of 60 sec. Analysis of the images was done using Xeleris 3.0 software provided by the manufacturer. Whole kidney region of interest (ROI) was drawn around the renal graft and used to calculate the parameters. Semilunar soft tissue background ROI was drawn at the inferolateral region of the graft. Iliac artery ROI was drawn at the iliac artery just distal to the renal graft. RS parameters analyzed include glomerular filtration rate (GFR_{DTPA}) obtained from Tc-99m DTPA RS, effective renal plasma flow rate (ERPF) obtained from Tc-99m MAG3 RS, as well as Hilson's perfusion index, time to peak, 20-min to peak ratio, and 20-min to 3-min ratio obtained from both Tc-99m DTPA and Tc-99m MAG3 RS.

2.3 Statistical analysis

Descriptive statistics were used to summarize the demographic characteristics and RS parameters. Receiver operating characteristic (ROC) curve analysis and the area under the ROC curve (AUC_{ROC}) using the logistic regression framework were used to determine the predictive power of RS parameters in predicting suboptimal renal function outcome at 1-year. DeLong's test was used to compare AUC_{ROC} of parameters derived from Tc-99m DTPA RS with corresponding parameters derived from Tc-99m MAG3 RS to determine which has better predictive performance. Spearman's correlation coefficient was used to determine the correlation between each scintigraphy parameter and the eGFR 1-year after transplantation as determined by the CKD-EPI equation. Analysis was conducted in R version 4.03 [13]. The 'pROC' package was used for the receiver operating characteristic curve analysis and comparison [14]. Figures were produced using the 'ggplot2' package [15].

3. Results

Between 1 June 2013 and 31 March 2019, among adult KT cases done in our center, a total of 298 patients underwent postoperative RS with Tc-99m DTPA and Tc-99m MAG3. Excluded were; one case with missing medical records, one case who underwent combined liver and kidney transplantation, three cases who died, and two cases who were lost to follow-up before the minimum follow-up time of 1 year. A total of 64 patients who underwent RS beyond 30 days of transplantation were also excluded. A total of 227 cases remained in the final analysis.

3.1 Patients

Details of patients' characteristics are presented in table 1. The average age of the 227 patients was 42.5 ± 10.5 years and 61.2% were males. Hypertension was the most common comorbidity found in 69.2% of patients. As the cause of ESRD, 33 (14.5%) patients had glomerulonephritis, while 45 (19.8%) patients had no other known underlying disease apart from ESRD. The most common mode of dialysis before KT was hemodialysis (74.0%) and the average duration of dialysis before KT was 4.8 ± 2.8 years. The preoperative serum creatinine was 10.8 ± 3.5 mg/dL. After transplantation, at 7-days, the average serum creatinine declined to 3.7 ± 3.5 mg/dL. Almost all patients underwent deceased donor kidney transplantation (94.3%), and the majority were from standard criteria donor (85.0%). The average donor age was 38.1 ± 12.6 years, the cold ischemic time was 16.7 ± 5.7 hours, and the operation time was 1.8 ± 0.5 hours. Details of transplantation is described in table 2.

Table 1 Patients' demographics presented as mean ± standard deviation unless otherwise indicated.

Characteristic	Mean ± SD
Number of patients	227
Age (years)	42.5 ± 10.5
Sex	
Male	139 (61.2%)
Female	88 (38.8%)
Weight (kg)	58.3 ± 11.6
Height (cm)	161.5 ± 7.8
BMI (kg/m2)	22.3 ± 3.8
Underlying diseases (%)	
Hypertension	157 (69.2%)
Diabetes mellitus	22 (9.7%)
SLE	5 (2.2%)
Renal stone	15 (6.6%)
Glomerulonephritis	33 (14.5%)
IgA nephropathy	20 (8.8%)
Gout	23 (10.1%)
ADPKD	5 (2.2%)
Dialysis duration before KT (years)	4.8 ± 2.8
Dialysis mode before KT	
Peritoneal dialysis	59 (26.0%)
Hemodialysis	168 (74.0%)
Preoperative SCr (mg/dL)	10.8 ± 3.5
SCr 7-days post-transplantation (mg/dL)	3.7 ± 3.5

Abbreviations: SD, standard deviation; BMI, body mass index; SLE, systemic lupus erythematosus; ADPKD, Autosomal dominant polycystic kidney disease; KT, kidney transplantation; BUN, blood urea nitrogen; SCr, serum creatinine.

Table 2 Kidney transplant characteristics presented as mean ± standard deviation unless indicated otherwise.

Characteristic	Mean ± SD
Type of transplant	
Deceased donor	214 (94.3%)
Living donor	13 (5.7%)
Type of donor	
Standard criteria donor	193 (85.0%)
Expanded criteria donor	34 (15.0%)
Donor age (years)	38.1 ± 12.6
Operation time (h)	1.8 ± 0.5
Cold ischemic time (h)	16.7 ± 5.7

3.2 Renal function after transplantation

After transplantation, renal function was assessed serially by measurement of serum creatinine used for calculation of eGFR by the CKD-EPI equation. The eGFR at 7 days, 1 month, 3 months, 6 months, and 1 year after transplantation were 39.3 ± 31.0 mL/min, 53.7 ± 23.6 mL/min, 55.5 ± 19.1 mL/min, 55.8 ± 18.7 mL/min, and 64.2 ± 19.7 mL/min, respectively, as shown in figure 1. At 1-year, 171 (75.3%) of patients had serum

creatinine ≤ 1.5 mg/dL (1.15 ± 0.20 mg/dL) and were deemed to have good renal function whereas 56 (24.7%) had values of > 1.5 mg/dL (2.18 ± 1.29 mg/dL) and were deemed to have suboptimal renal function [1].

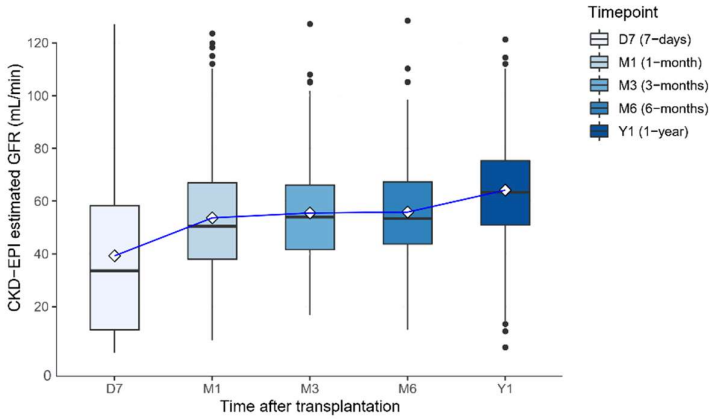

Figure 1 Boxplots of CKD-EPI estimated GFR at 7 days, 1 month, 3 months, 6 months, and 1 year after kidney transplantation.

3.3 Renal scintigraphy

Each patient underwent RS between 1 – 30 days after kidney transplantation with a median time of 6 days (interquartile range; IQR 3 to 13 days). The quantitative parameters are presented in table 3. From Tc-99m DTPA RS, the median and IQR of GFR_{DTPA}, Hilson's perfusion index, time to peak, 20-min to peak ratio, 20-min to 3-min ratio were 34.3 mL/min (20.4 – 61.1), 94.4 (68.1 – 135.8), 2.0 mins (1.4 – 2.7), 58.0% (49.0 – 69.0), and 65.0% (56.0 – 77.0), respectively. From Tc-99m MAG3 RS, the median and IQR of ERPF, Hilson's perfusion index, time to peak, 20-min to peak ratio, 20-min to 3-min ratio were 183.6 mL/min (130.5 – 244.3), 95.6 (74.9 – 124.2), 3.4 mins (2.0 – 19.7), 81.0% (56.0 – 98.0), and 86.5% (59.0 – 136.0), respectively.

Table 3 Values of renal scintigraphy parameters after transplantation.

Parameter	Median (IQR)*
Tc-99m DTPA renal scintigraphy	
GFR_{DTPA} (mL/min)	34.3 (20.4 – 61.1)
Hilson's perfusion index	94.4 (68.1 – 135.8)
Time to peak (mins)	2.0 (1.4 – 2.7)
20-min to peak ratio (%)	58.0 (49.0 – 69.0)
20-min to 3-min ratio (%)	65.0 (56.0 – 77.0)
Tc-99m MAG3 renal scintigraphy	
ERPF (mL/min)	183.6 (130.5 – 244.3)
Hilson's perfusion index	95.6 (74.9 – 124.2)
Time to peak (mins)	3.4 (2.0 – 19.7)
20-min to peak ratio (%)	81.0 (56.0 – 98.0)
20-min to 3-min ratio (%)	86.5 (59.0 – 136.0)

Abbreviations: IQR, interquartile range; GFR, glomerular filtration rate; ERPF, effective renal plasma flow rate.
*Most data have skewed distribution, thus are presented as median and interquartile range instead of mean and standard deviation.

3.4 Renal scintigraphy parameters and 1-year renal function outcome

To determine performance of RS parameters for predicting suboptimal 1-year renal function outcome as defined by serum creatinine > 1.5 mg/dL, ROC curve analysis was performed, and the results are presented in table 4 and figure 3. The predictiveness of the parameters was at most only moderate with ERPF obtained from Tc-99m MAG3 RS having the highest AUC_{ROC} of 0.71 (95% CI. 0.64 to 0.79). The predictor that was the poorest in predicting the outcome was the time to peak obtained from Tc-99m DTPA RS with an AUC_{ROC} of 0.53 (95% CI. 0.43 to 0.62). DeLong's test revealed that there was no significant difference between any pair of parameters from Tc-99m DTPA RS and Tc-99m MAG3 RS. Although statistically not significant, the AUC_{ROC} of Tc-99m MAG3 RS parameters do show trends of being more predictive than those obtained from Tc-99m DTPA RS.

Table 4 Comparison of quantitative renal scintigraphy parameters between Tc-99m DTPA and Tc-99m MAG3 in predicting suboptimal 1-year renal function outcome as defined by serum creatinine > 1.5 mg/dL.

Parameter	AUC_{ROC}	95% CI.	P_{DeLong}*
Quantified function			0.30
Tc-99m DTPA (GFR_{DTPA}, mL/min)	0.69	0.62, 0.76	
Tc-99m MAG3 (ERPF, mL/min)	0.71	0.64, 0.79	
Hilson's perfusion index			0.28
Tc-99m DTPA	0.61	0.52, 0.70	
Tc-99m MAG3	0.66	0.58, 0.74	
Time to peak (min)			0.27
Tc-99m DTPA	0.53	0.43, 0.62	
Tc-99m MAG3	0.59	0.50, 0.70	
20-min to peak ratio (%)			0.06
Tc-99m DTPA	0.54	0.46, 0.63	
Tc-99m MAG3	0.63	0.55, 0.71	
20-min to 3-min ratio (%)			0.35
Tc-99m DTPA	0.59	0.51, 0.68	
Tc-99m MAG3	0.63	0.55, 0.71	

Abbreviations: GFR, glomerular filtration rate; ERPF, effective renal plasma flow rate; AUC_{ROC}, area under receiver operating characteristic curve. *P_{DeLong} is the P-value from DeLong's test comparing AUC_{ROC} of parameters derived from Tc-99m DTPA and Tc-99m MAG3 renal scintigraphy.

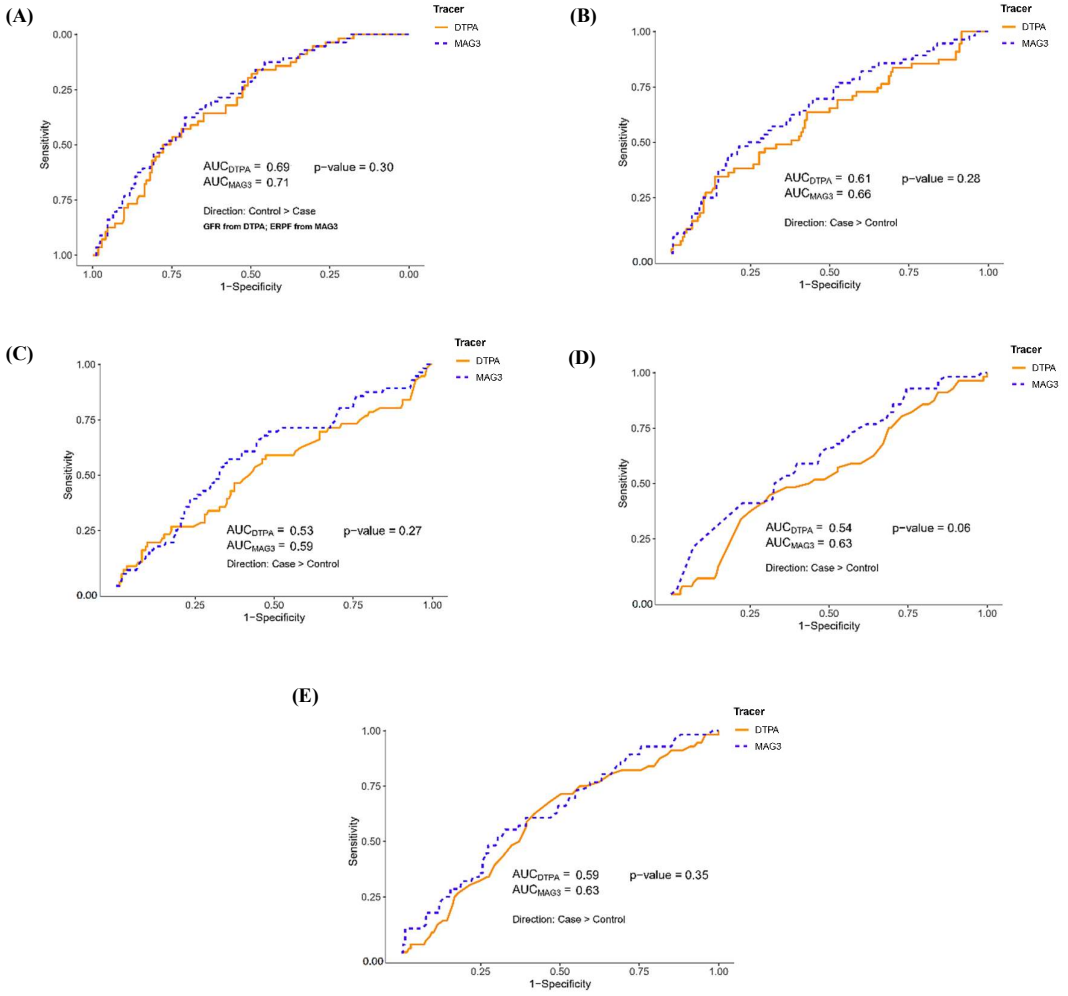

Figure 2 Receiver operating characteristic curves of quantified renal scintigraphy parameters from Tc-99m DTPA and Tc-99m MAG3 renal scintigraphy in prediction of the renal function at one year after transplantation; (A) DTPA (GFR) vs. MAG3 (ERPF), (B) Hilson's perfusion index, (C) Time to peak accumulation, (D) 20-min to peak ration, and (E)20-min to 3 min ratio. *p*-values of DeLong's test for comparing areas under curve are provided for each plot.

Correlation between post-transplantation RS parameters and eGFR by the CKD-EPI equation at 1-year after KT are presented in table 5. Overall, the correlation was at best only weak. Quantified function, i.e., GFR_{DTPA} from Tc-99m DTPA RS and ERPF from Tc-99m MAG3 RS did not have significantly different correlation with eGFR (ρ, 0.28 vs. 0.31). Similarly, Hilson's perfusion index obtained from RS using either radiopharmaceutical had similar correlation with eGFR (ρ, -0.16 vs. -0.21). There were three parameters which had significantly better correlation with eGFR when obtained from Tc-99m MAG3 RS as opposed to when they were obtained from Tc-99m DTPA RS. These include the time to peak (ρ, -0.18 vs. 0.07), 20-min to peak ratio (ρ, -0.25 vs. -0.05), and 20-min to 3-min ratio (ρ, -0.24 vs. -0.11).

Table 5 Correlation between post-transplant renal scintigraphy parameters and estimated GFR by the CKD-EPI equation at 1-year after transplantation.

Parameters	Spearman's ρ	$P_{Spearman}$*	$P_{Williams}$**
Quantified function			0.39
Tc-99m DTPA (GFR)	0.28	<0.001	
Tc-99m MAG3 (ERPF)	0.31	<0.001	
Hilson's perfusion index			0.93
Tc-99m DTPA	-0.16	0.015	
Tc-99m MAG3	-0.21	0.001	
Time to peak			0.003
Tc-99m DTPA	0.07	0.25	
Tc-99m MAG3	-0.18	0.005	
20-min to peak ratio			0.002
Tc-99m DTPA	-0.05	0.43	
Tc-99m MAG3	-0.25	<0.001	
20-min to 3-min ratio			0.003
Tc-99m DTPA	-0.11	0.10	
Tc-99m MAG3	-0.24	<0.001	

Abbreviations: GFR, glomerular filtration rate; ERPF, effective renal plasma flow rate. *$P_{Spearman}$ is the P-value of the Spearman's correlation test for each correlation coefficient. **$P_{Williams}$ is the P-value of from Williams' test for comparing two dependent correlation coefficients sharing one variable, i.e., comparing the correlation coefficient between Tc-99m DTPA parameter with CKD-EPI eGFR with corresponding correlation coefficient between Tc-99m MAG3 parameter with CKD-EPI eGFR.

4. Discussion

In this retrospective study, we aimed to compare the capability of two RS radiopharmaceuticals, Tc-99m DTPA and Tc-99m MAG3, for predicting renal function 1-year after KT. RS is traditionally used to evaluate acute complications and graft function early after KT, but there have also been several studies that evaluated the association between RS findings and late graft failure [16,17] as well as long-term graft function determined by serum creatinine [11]. Few studies have directly compared Tc-99m DTPA RS and Tc-99m MAG3 RS in predicting and correlation with long-term renal function outcomes. A previous study compared Tc-99m DTPA RS and Tc-99m MAG3 RS in terms of predicting early graft dysfunction [18], however, to our knowledge, this is one of the first studies to compare directly between RS using Tc-99m DTPA and Tc-99m MAG3 in predicting long-term renal function.

The AUC_{ROC} of Hilson's perfusion index derived from two radiopharmaceuticals were not significantly different in predicting 1-year suboptimal renal function and had similar negative correlation with eGFR at 1-year. This is not surprising because perfusion is assessed during the first 60 sec and is less impacted by functional radiopharmaceutical kinetics. The negative correlation is most likely because a higher perfusion index value is associated with either acute rejection or transplant renal artery stenosis which are conditions related to poorer graft outcome and function [19].

Quantified function in terms of GFR_{DTPA} from Tc-99m DTPA RS and ERPF from Tc-99m MAG3 RS were not significantly different in predicting 1-year renal function outcome and had no significantly different positive correlation with eGFR at 1-year. This is likely because estimation of GFR_{DTPA} and ERPF are both obtained based on the same measure, i.e., the degree of accumulation of the radiopharmaceutical at the early phase of the renogram before beginning of the excretory phase [20,21].

For three parameters including time to peak, 20-min to peak ratio, and 20-min to 3-min ratio, even though there were no significant differences in predictiveness of suboptimal renal function between Tc-99m DTPA RS and Tc-99m MAG3 RS, but these parameters show significantly better correlation with eGFR at 1-year when they were derived from Tc-99m MAG3 RS as compared with corresponding parameters from Tc-99m DTPA RS. A recent study showed that subclinical tubulitis in the early post-transplantation period was associated with a higher incidence of subsequent T-cell mediated rejection as well as poorer renal function [22]. Time to peak, 20-min to peak ratio, and 20-min to 3-min ratio in Tc-99m MAG3 RS are all associated with cortical retention of the radiopharmaceutical because Tc-99m MAG3 is a tubular-secreting agent. This could explain why these parameters were better correlated with eGFR than corresponding parameters from Tc-99m DTPA RS since Tc-99m DTPA is excreted by glomerular filtration.

Our study has several limitations. Because of the retrospective nature, there is variation of the timing of post-transplantation RS and to maintain a reasonable sample size, RS performed within a rather wide time window of 30 days after transplantation had to be allowed. The residual activity at the end of the Tc-99m DTPA RS may interfere with the Tc-99m MAG3 RS, which was done immediately after Tc-99m DTPA RS. However, the interference should not significantly impact the results since the dose of Tc-99m MAG3 was 5 times higher than that of Tc-99m DTPA which should negate the small amount of shine-through from the end of the Tc-99m DTPA study.

5. Conclusion

Although in terms of predictiveness, no difference was found between parameters obtained from Tc-99m DTPA RS and Tc-99m MAG3 RS, but time to peak, 20-min to peak ratio, and 20-min to 3-min ratio had better correlation with 1-year post-transplant eGFR when obtained from Tc-99m MAG3 RS compared with corresponding parameters obtained from Tc-99m DTPA RS. Tc-99m MAG3 should be the preferred radiopharmaceutical for assessment of post-transplantation renal graft function as its parameters are more correlated with long-term renal function.

6. Ethical approval

This retrospective study was approved by the Khon Kaen University Ethics Committee for Human Research (Ref. HE631182). Since all data were obtained from available medical records and imaging database, requirement for obtaining informed consent was waived. Research methods conformed to the ethical guidelines of the 1975 and later iterations of the Declaration of Helsinki.

7. Acknowledgements

We would like to acknowledge Professor Yukifumi Nawa, for editing the MS via KKU Publication Clinic, Thailand. This research received no specific grant or financial support from any funding agency in the public, commercial, or not-for-profit sectors.

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