Tc-99m Hydroxymethylene Diphosphonate (HMDP) Renal Uptake as a Surrogate Marker of Postoperative Impairment of the Glomerular Filtration Rate in Renal Tumor Patients Following Nephron-Sparing Surgery

Hongyoon Choi · Won Woo Lee · Young So ·
Seunggyun Ha · Seok-Soo Byun · Sang Eun Kim

Received: 18 March 2014 / Revised: 17 May 2014 / Accepted: 22 May 2014 / Published online: 11 June 2014
© Korean Society of Nuclear Medicine 2014

Abstract Purpose: We investigated Tc-99m hydroxymethylene diphosphonate (HMDP) scintigraphy findings in renal tumor patients from the perspective of postoperative renal dysfunction following nephron-sparing surgery (NSS). Methods: Forty-three renal tumor patients (M:F = 28:15, age 53.9 ± 12.5 years) who had undergone Tc-99m HMDP scintigraphy after NSS were enrolled. The patients were divided into HMDP⁺ or HMDP⁻ groups by visual assessment, and the asymmetric index (ASI) was calculated using a region-of-interest analysis. In 16 patients, the total and split glomerular filtration rate (GFR) was assessed using Tc-99m diethylenetriaminepentaacetic acid (DTPA) scintigraphy at baseline and at 3 and 6 months post-NSS. Results: High Tc-99m HMDP uptake was observed in the operated kidneys, but this did not persist later than 7 days post-NSS. Split GFR of the operated kidneys at baseline (58.5 ± 9.3 ml/min) was significantly reduced at 6 months post-NSS (40.1 ± 5.9 ml/min, $p < 0.001$) in only those who showed intense uptake of Tc-99m HMDP. Declines in both total GFR ($p = 0.010$ and $p =$

0.002 for 3 and 6 months, respectively) and split GFR of the operated kidneys ($p < 0.001$ and $p < 0.001$ for 3 and 6 months, respectively) were clearly evidenced at 3 and 6 months post-NSS only in patients with high Tc-99m HMDP in the operated kidneys. The ASI was negatively correlated with %change in the split GFR of these operated kidneys at 6 months post-NSS ($\rho = -0.578$, $p = 0.0304$). Conclusions: Tc-99m HMDP uptake within 1 week following NSS is a surrogate marker of GFR impairment over 6 months post-NSS.

Keywords Tc-99m phosphonate · Scintigraphy · Glomerular filtration rate · Nephrectomy

Introduction

Nephron-sparing surgery (NSS) has become the standard procedure for treating small renal tumors. Without the expense of cancer control, nephron-sparing partial nephrectomy can effectively preserve postoperative renal function, which is an important issue in urology [1, 2]. Many clinical and surgical factors are known to affect postoperative renal function, including age, sex, solitary kidney, underlying chronic kidney disease, tumor size, ischemic time during renal artery clamping, and extent of resected healthy tissue [3–5]. Of the controllable factors that affect postoperative renal function, warm ischemic time and perioperative parenchymal damage are of most concern. Recent advances in surgical techniques and awareness of the consequences of renal ischemia have reduced or eliminated inadvertent prolonging of ischemic time, and modern NSS usually takes less than 30 min [5, 6]. In fact, a warm ischemic time of less than 20 min is recommended for effective NSS [6]. However, some degree of ischemic injury during renal artery clamping is unavoidable,

H. Choi · W. W. Lee (✉) · S. Ha · S. E. Kim
Department of Nuclear Medicine, Seoul National University
Bundang Hospital, 173-82 Gumi-ro, Bundang-gu, Seongnam-si,
Gyeonggi-do, 463-707 Seoul, Republic of Korea
e-mail: wwlee@snu.ac.kr

S.-S. Byun
Department of Urology, Seoul National University Bundang
Hospital, Seoul National University College of Medicine, Seoul,
Republic of Korea

W. W. Lee · S. E. Kim
Institute of Radiation Medicine, Medical Research Center, Seoul
National University, Seoul, Republic of Korea

Y. So
Department of Nuclear Medicine, Konkuk University School of
Medicine, Seoul, Republic of Korea

even with a relatively short ischemic period [7]. Furthermore, damage/loss of surrounding renal parenchymal tissue is also unavoidable because a sufficient resection margin is required for cancer surgery. Therefore, identification of a surrogate marker of perioperative renal tissue injury could facilitate the development of a more minimally invasive surgical technique in this era of rapid NSS.

Extrasosseous uptake of Tc-99m-labeled phosphorus agents has been described in a variety of soft tissue diseases [8, 9]. Ischemic injury and subsequent calcium deposition are considered to be associated with Tc-99m-labeled phosphorus agent uptake [10, 11]. Furthermore, ischemia and reperfusion via renal arteries have been reported to generate renal uptake of Tc-99m-labeled phosphorus agents [12, 13]. In the clinical setting of nephron-sparing partial nephrectomy among renal tumor patients, Tc-99 phosphonate scintigraphy readily demonstrated transient uptake of Tc-99m phosphonate in operated kidneys [14]. However, there has been no follow-up report of image-based prediction of glomerular filtration rate (GFR) impairment post-NSS. Thus, in the current study, we retrospectively reviewed Tc-99m hydroxymethylene diphosphonate (HMDP) bone scintigrams and Tc-99m diethylenetriaminepentaacetic acid (DTPA) GFR scintigrams of renal tumor patients following partial nephrectomy. We attempted to determine the quantitative relationship between the degree of Tc-99m HMDP uptake and functional deterioration of the operated kidneys post-NSS.

Materials and Methods

Subjects and Clinical Factors

From July 2009 to August 2013, 218 renal tumor patients underwent both partial nephrectomy and Tc-99m HMDP bone scintigraphy at our hospital. Tc-99m HMDP bone scintigraphy is routinely performed as a work-up test for patients at our institution, particularly among those with renal cell carcinoma. As the timing of bone scintigraphy is not strictly specified, and due to the excessive workload of our large tertiary medical center, 43 patients could not undergo bone scintigraphy preoperatively but experienced bone scintigraphy within 1 month post partial nephrectomy. These 43 patients were enrolled in the current study (Fig. 1). Table 1 summarizes the demographic characteristics of these patients. Medical record and scintigraphy findings were retrospectively reviewed. The current study was reviewed and approved by the institutional ethics review board (IRB no. = B-1310/224-103).

Tc-99m HMDP Bone Scintigraphy

No specific preparation was required for Tc-99m HMDP scintigraphy. Patients were injected intravenously with 1,295 MBq (35 mCi) of Tc-99m HMDP (HDP, Mallinckrodt, St. Louis, MO, USA). Thereafter, they drank water (at least 500 ml) and voided frequently until image acquisition in order to reduce unnecessary radiation exposure. Whole-body images from the vertex to the feet were obtained 3 h after injection using a dual-head gamma camera system (Forte, ADAC-Philips, Holt, MO, USA) equipped with a low-energy high-resolution collimator. The acquisition window (20 %) was set at an energy peak of 140 KeV, and the image matrix was 1,024×1,024.

Image Analysis

First, we visually assessed renal parenchymal Tc-99m HMDP uptake and divided the patients into two groups: HMDP⁺ and HMDP⁻. The renal parenchymal activity of the operated kidneys was compared visually with that of the contralateral kidneys. HMDP⁺ patients were defined as those with renal parenchymal Tc-99m HMDP uptake greater than the contralateral kidney and increased parenchymal Tc-99m HMDP activity involving at least one-third of the corresponding kidney. Patients with renal parenchymal activity equal to or lower than the contralateral kidney or those with Tc-99m HMDP activity involving less than one-third of the corresponding kidney were classified as HMDP⁻.

Second, we performed a quantitative analysis of renal parenchymal Tc-99m HMDP uptake using posterior images. Regions of interest (ROIs) were drawn along the renal contours over the operated and contralateral kidneys (Fig. 2). We carefully excluded renal pelvic radioactivity with the aid of postoperative abdomino-pelvic contrast-enhanced computed tomography (CT). Background ROIs were drawn at the inferior-lateral aspect of the corresponding kidneys. The asymmetric index (ASI) was used to represent the renal uptake of the operated kidney relative to that of the contralateral non-operated kidney and was defined as:

Asymmetric index (ASI)

$$= \frac{\text{Operated Kidney} \left(\frac{\text{counts}}{\text{pixel}} \right) - \text{Op. Background} \left(\frac{\text{counts}}{\text{pixel}} \right)}{\text{Contralateral kidney} \left(\frac{\text{counts}}{\text{pixel}} \right) - \text{Contralat. Background} \left(\frac{\text{counts}}{\text{pixel}} \right)}$$

Fig. 1 Flowchart of subjects selection

The quantitative parameter was assessed using ImageJ software (Version 1.47 t, <http://rsb.info.nih.gov/ij/>, National Institutes of Health, Bethesda, MD, USA).

Tc-99m DTPA GFR Scintigraphy

We recently established a revised Gates' GFR scintigraphic method that substantially improves the reproducibility and accuracy of the GFR measurement of individual kidneys [15]. Briefly, in the present study, the patients were instructed to ingest 500 ml of water 30 min before imaging. Serial dynamic images were then acquired for 20 min starting from the injection of 185 MBq (5 mCi) Tc-99m DTPA (TechneScan® DTPA,

Mallinckrodt, St. Louis, MO, USA) with the patient in the supine position and the detector positioned posteriorly 30 cm away from the patient. A single-head gamma camera (Argus, ADAC/Philips, Holt, MO, USA) equipped with a low-energy high-resolution collimator was used for GFR scintigraphy with a 20 % energy window set at an energy peak of 140 KeV. The image matrix was 128×128. Measurement of the injected radioactive counts and the area under the curve (AUC) of the renogram at 2–3-min post-injection enabled determination of the percent renal uptake for each individual kidney. The original Gates' GFR equation [16], $GFR (ml/min) = (\%renal\ uptake \times 9.8127) - 6.82519$, was revised to $GFR (ml/min) = (\%renal\ uptake \times 11.7773) -$

Table 1 Patient clinical characteristics (*n*=43)

	Mean ± standard deviation
Age (years)	53.9±12.5 (range 24–82)
Sex (male:female)	28:15
Interval between operation and Tc-99m HMDP scan (days)	4.5±3.2 (range 1–17)
sCr_preoperative (mg/dl)	0.91±0.20
eGFR_preoperative (ml/min/1.73 m ²)	85.0±17.2
Tumor type	RCC 39, angiomyolipoma 1, oncocytoma 1, mixed epithelial and stromal tumor 1, simple cyst 1
Tumor size (cm)	3.0±1.60
Partial nephrectomy procedure	Open, 21; robot-assisted, 20; laparoscopic, 2

sCr: serum creatinine

eGFR: estimated glomerular filtration rate

RCC: renal cell carcinoma

Fig. 2 How to draw regions of interest (ROIs) for the asymmetric index (ASI). A posterior view Tc-99m HMDP scintigraphy image was used for the analysis. Please note that the upper pole of the left kidney has a defect due to a previous partial nephrectomy and the remaining renal parenchyma shows increased uptake of Tc-99m HMDP

0.7354 in our previous report [15], and this revised equation was employed in the present study. Of the 43

patients, 16 underwent Tc-99m DTPA GFR scintigraphy at baseline as well as at 3 and 6 months postoperatively (Fig. 1).

Statistical Analysis

In order to determine postoperative functional deterioration, we calculated the percentage change in GFR, which was defined as:

$$\% \text{change in GFR} = \frac{(GFR \text{ post 3 or 6 mo} - GFR \text{ pre})}{GFR \text{ pre}} \times 100$$

where GFR post was measured 3 or 6 months postoperatively, and GFR pre was obtained preoperatively. The serum creatinine (sCr) level and estimated GFR (eGFR) derived from the MDRD equation [17, 18] were also analyzed to determine the percentage change. All data are presented as the mean $\pm$ standard deviation. The chi-square test was used to analyze categorical variables, including clinical characteristics, and Mann-Whitney tests were used to compare parameters between the HMDP⁺ and HMDP⁻ groups. Wilcoxon paired tests

Fig. 3 The time course of Tc-99m HMDP uptake in the operated kidneys. **a** The ASI (asymmetric index) was greater in the early stages, that is, within 1 week, compared with later time points. There was a significant negative correlation between the ASI and the interval between the operation and bone scintigraphy ($r = -0.3297$, $p = 0.0309$). **b** and **c** Follow-up bone scintigraphy in a 45-year-old female patient with renal cell carcinoma (RCC) in the right kidney. **b** Preoperative CT revealed a small

(1.1 cm) RCC in the mid-portion of the right kidney (red arrow). Postoperative bone scintigraphy was performed at day 3 post partial nephrectomy. Anterior and posterior bone scintigrams clearly show the small defect and surrounding intense uptake of Tc-99 m HMDP in the right kidney. **c** Follow-up CT and bone scintigraphy were performed 6 months postoperatively. The RCC mass was successfully removed, and the initial Tc-99m HMDP uptake disappeared in the follow-up bone scintigrams

Table 2 Tc-99m DTPA GFR scintigraphy findings among 16 patients

		HMDP ⁻ (n=5)	HMDP ⁺ (n=11)	P value
Total GFR	Preoperative (ml/min/1.73 m ²)	121.6±12.0	121.9±16.1	0.9548
	Postoperative-3 months (ml/min/1.73 m ²)	120.4±19.6	108.8±13.0	0.2342
	Postoperative-6 months (ml/min/1.73 m ²)	119.1±16.4	107.2±9.8 (n=9)	0.2053
	%change total GFR_postoperative 3 months (%)	-1.3±8.5	-10.1±1.0	0.0616
	%change total GFR_postoperative 6 months (%)	-1.9±10.0	-14.7±7.8 (n=9)	0.0196*
Split GFR	Op_preoperative (ml/min)	62.3±12.7	58.5±9.3	0.6102
	Op_postoperative 3 months (ml/min)	57.0±18.2	44.1±6.5	0.1004
	Op_postoperative 6 months (ml/min)	56.4±19.7	40.1±5.9 (n=9)	0.0388*
	%change op GFR_postoperative 3 months (%)	-9.4±14.4	-23.7±12.8	0.0474*
	%change op GFR_postoperative 6 months (%)	-10±19.2	-33.4±11.1 (n=9)	0.0278*
	Con_preoperative (ml/min)	62.0±13.7	66.6±10.6	0.5332
	Con_postoperative 3 months (ml/min)	66.8±13.8	66.6±9.7	0.8651
	Con_post 6 mo (ml/min)	65.3±6.9	66.7±10.3 (n=9)	0.9468
	%change of con GFR_postoperative 3 months (%)	8.2±4.3	0.75±11.3	0.3356
	%change of con GFR_postoperative 6 months (%)	8.1±15.7	1.2±11.5 (n=9)	0.5485
Surgical parameters	Tumor size (cm)	1.96±1.04	3.24±1.56	0.0791
	Operation time (min)	158.3±46.5 (n=3)	116.1±53.1 (n=8)	0.2616
	Warm ischemia time (min)	16.6±3.12	19.2±9.31 (n=10)	0.8058
	EBL (ml)	75.0±35.4 (n=2)	164.3±114.4 (n=7)	0.3758
Tc-99m HMDP scan	ASI	1.22±0.22	3.01±2.20	0.0039*

Data are mean ± standard deviation. *GFR*, glomerular filtration rate; *EBL*, estimated blood loss; *ASI*, asymmetric index; *Op*, operated kidney; *Con*, contralateral kidney. *Statistically significant difference

were employed to compare pre- and postoperative GFR parameters. A repeated measure ANOVA was used for the serial GFR data analysis. Pearson's or Spearman's coefficients were obtained for the parametric or non-parametric correlation analyses, respectively. The analyses were performed using STATA version 12.0.0 statistical software, and a *p* value < 0.05 was considered statistically significant.

Results

Time Course of Tc-99m HMDP Uptake Following Partial Nephrectomy

In our initial investigation, we attempted to determine the time course of Tc-99m HMDP uptake in the operated kidneys following partial nephrectomy. The quantitative parameter ASI, which indicates asymmetrically increased Tc-99m HMDP uptake in the operated kidney compared with the contralateral kidney, was used for objective determination of Tc-99m HMDP uptake. The ASI had a significant negative correlation ($r = -0.3297$, $p = 0.0309$) with the time interval between the operation and bone scintigraphy, which means that Tc-99m HMDP uptake was greater during the early post-NSS period, that is, within 1 week (Fig. 3a).

Of the 43 patients, 8 (male:female=5:3, age 55.0 ± 10.5 years) underwent follow-up bone scintigraphy at 6 months ($n=7$) or 1 year ($n=1$) after the initial postoperative bone scintigraphy. The initial high Tc-99m HMDP uptake observed in the operated kidneys disappeared in all eight patients at the follow-up bone scintigraphy (Fig. 3b and c). In addition, the ASI at the initial bone scintigrams (2.74 ± 0.75) was significantly decreased at the follow-up bone scintigrams (1.05 ± 0.28 , $p = 0.0078$).

Tc-99m HMDP Uptake as a Surrogate Marker of Postoperative GFR Impairment

Next, we investigated the clinical implication of early Tc-99m HMDP uptake following partial nephrectomy. Sixteen patients who underwent Tc-99m DTPA GFR scintigraphy 1 week (7.4 ± 8.5 days) prior to surgery (baseline) as well as 3 months (97.9 ± 24.5 days) and 6 months (197.0 ± 28.3 days) postoperatively were included in this analysis (Fig. 1). All underwent Tc-99m HMDP bone scintigraphy within 1 week (4.3 ± 1.7 days, range 2–7 days) postoperatively; the patients were allocated to the HMDP⁻ group ($n=5$) or HMDP⁺ group ($n=11$) based on a visual analysis (Table 2).

Fig. 4 Serial GFR data plotting. The HMDP⁺ patients experienced GFR impairment at 3 and 6 months postoperatively, whereas the HMDP⁻ patients did not undergo any significant GFR change. At 3 and 6 months postoperatively, total GFR was significantly lower in the HMDP⁺ group compared with the baseline total GFR ($p=0.010$ and $p=0.002$ for 3 and

6 months postoperatively). The split GFR of the operated kidneys in the HMDP⁺ group showed a GFR decline during the early postoperative period (3 months, $p<0.001$), and this was further decreased at 6 months postoperatively ($p<0.001$). * $p<0.05$, ** $p<0.005$, *** $p<0.001$

There was no difference between the HMDP⁻ and HMDP⁺ groups in the preoperative total or split GFR ($p>0.05$). The total GFR gradually decreased from baseline (121.9 ± 16.1 ml/min/1.73 m²) to 3 months (108.8 ± 13.0 ml/min/1.73 m²) and 6 months (107.2 ± 9.8 ml/min/1.73 m²) postoperatively in the HMDP⁺ group, but remained similar in the HMDP⁻ group (121.6 ± 12.0 ml/min/1.73 m² preoperatively versus 120.4 ± 19.6 ml/min/1.73 m² at 3 months and 119.1 ± 16.4 ml/min/1.73 m² at 6 months postoperatively). The percent change in total GFR 3 months postoperatively was -10.1 ± 1.0 % in the HMDP⁺ group, which was marginally significantly greater than the -1.3 ± 8.5 % in the HMDP⁻ group ($p=0.0616$). However, at 6 months postoperatively, the percent change in total GFR in the HMDP⁺ group (-14.7 ± 7.8 %) was significantly greater than that in the HMDP⁻ group (-1.9 ± 10.0 %) ($p=0.0196$) (Table 2).

Regarding the split GFR of the operated kidneys, not only the percent change but also the absolute value was significantly lower (40.1 ± 5.9 ml/min) in the HMDP⁺ group compared

with the HMDP⁻ group (56.4 ± 19.7 ml/min) ($p=0.0388$) at 6 months postoperatively. The percent change in split GFR at 3 and 6 months postoperatively was -23.7 ± 12.8 % and -33.4 ± 11.1 %, respectively, in the HMDP⁺ group. These values were significantly greater than the -9.4 ± 14.4 % ($p=0.0474$) and -10 ± 19.2 % ($p=0.0278$), respectively, in the HMDP⁻ group (Table 2).

On the other hand, the split GFR of the contralateral kidney did not differ significantly between the HMDP⁺ and HMDP⁻ groups in terms of both the absolute value of GFR and the percentage change at 3 and 6 months postoperatively ($p>0.05$) (Table 2).

Surgical parameters known to affect postoperative renal function, such as tumor size (cm), operation time (min), warm ischemia time (cm), and estimated blood loss (ml), were not significantly different between the HMDP⁺ and HMDP⁻ groups ($p>0.05$) (Table 2). However, the ASI, the bone scintigraphy parameter of Tc-99m HMDP uptake, was significantly higher in the

Fig. 5 A case showing high Tc-99m HMDP uptake during the immediate postoperative period and GFR impairment over the following 6 months. The 70-year-old female patient had a 3.1-cm renal cell carcinoma in the right kidney (red arrow) (a) and underwent a partial nephrectomy. At day 3 postoperatively, she underwent Tc-99m HMDP bone scintigraphy, and intense uptake of Tc-99m HMDP was observed with

an ASI of 9.41 (b). The Tc-99m DTPA GFR scintigrams clearly demonstrate impaired split GFR of the operated right kidney at 3 months (d) and 6 months (e) postoperatively compared with baseline split GFR (c). The blue arrows in panels (d) and (e) highlight the area-under-the-curve difference (that is, the split GFR difference) between the non-operated left kidney and operated right kidney after the partial nephrectomy

HMDP⁺ group (3.01 ± 2.20) compared with the HMDP⁻ group (1.22 ± 0.22) ($p=0.0039$) (Table 2).

Serial data plotting (Fig. 4) revealed the same GFR changes as the group comparisons (Table 2). The HMDP⁺ patients had significantly lower total GFRs at 3 and 6 months postoperatively compared with their preoperative total GFRs ($p=0.010$ and $p=0.002$ for 3 and 6 months postoperatively, respectively). However, there were no significant serial changes in total GFR among patients in the HMDP⁻ group ($p>0.05$). The split GFR of the operated kidney was significantly reduced from baseline at 3 months postoperatively ($p<0.001$) and was further reduced at 6 months postoperatively ($p<0.001$) in the HMDP⁺ group, whereas no significant serial change was observed among those in the HMDP⁻ group over 6 months postoperatively ($p>0.05$). No serial change in the split GFR of the contralateral kidney was observed among HMDP⁺ or HMDP⁻ patients ($p>0.05$) (Fig. 4). Representative cases are shown in Figs. 5 and 6.

Serum creatinine (sCr) levels and eGFR were also analyzed among the 16 patients who underwent Tc-99m DTPA GFR scintigraphy. No significant difference

between the HMDP⁺ and HMDP⁻ patients was observed for either of these factors at all the time points. Furthermore, no significant percent change in either sCr or eGFR was detected over the 6-month postoperative period among the HMDP⁺ and HMDP⁻ patients (Table 3).

Correlation Between the Bone Scintigraphy Parameter (ASI) and GFR Impairment

ASI, the bone scintigraphy parameter assessed in the current study, was used to objectively determine Tc-99m HMDP uptake in the operated kidneys (Figs. 2 and 3). Among the 16 patients who underwent Tc-99m DTPA GFR scintigraphy, the presence of Tc-99m HMDP uptake was associated with GFR impairment, but the other parameters were not (Table 2). Thus, we tested the correlation between ASI and GFR changes to investigate quantitative relationships between these variables. Percent changes in total and split GFR of the operated kidneys were investigated. As a result, the ASI was found to be negatively correlated with the percent

Fig. 6 A case demonstrating low Tc-99m HMDP uptake during the immediate postoperative period and GFR preservation over the 6-month follow-up period. The 51-year-old male patient had a 2.5-cm renal cell carcinoma in the left kidney (red arrow) (a) and underwent a partial nephrectomy 4 days prior to the Tc-99m HMDP bone scintigraphy. No intense Tc-99m HMDP uptake was observed in the operated left kidney,

which had an ASI of 0.94 (b). Tc-99m DTPA GFR scintigrams performed at baseline (c) and 3 months (d) and 6 months (e) post-NSS reveal preserved GFR of the operated left kidney. Please note that no significant difference in the area under the curve was observed between the operated left kidney and the contralateral right kidney over the 6 months postoperatively

change in GFR of the operated kidneys at 6 months postoperatively ($\rho = -0.578$, $p = 0.0304$).

Discussion

Renal uptake of Tc-99m-labeled phosphorus agents has been well described in animal and human diseases that involve renal ischemia [11–13]. Recent enthusiasm for nephron-sparing partial nephrectomy in renal tumor patients has raised interest in potential surrogate markers of renal damage during renal artery clamping and subsequent release [1–3, 5]. As a matter of fact, it is not surprising to observe high Tc-99m phosphonate uptake in the operated kidneys following renal artery clamping during partial nephrectomy [14] because the relationship between ischemic injury and Tc-99m phosphate uptake has been well described in the literature [10]. Elevated intracellular calcium level after ischemic injury caused by renal artery clamping is associated with Tc-99m phosphonate uptake and the subsequent reperfusion

(i.e., release of renal artery clamping) can also cause further damage giving rise to retention of Tc-99m phosphonate in the operated kidney [10, 11]. However, the clinical implications of Tc-99m phosphonate uptake in the operated kidneys remain elusive. The first clinical report of renal uptake of Tc-99m phosphonate during partial nephrectomy described the time course of Tc-99m phosphonate uptake in just 11 patients [14]. In the present study, the clinical implications of early Tc-99m HMDP uptake as well as the time course of Tc-99m HMDP uptake were investigated with a larger cohort of renal tumor patients. Furthermore, regarding functional impairment, the specific GFR values of the affected kidneys could be accurately evaluated using Tc-99m DTPA GFR scintigraphy [15, 19]. As a result, Tc-99m HMDP uptake in the operated kidneys during immediate postoperative bone scintigraphy turned out to be a useful imaging marker of perioperative renal injury leading to GFR impairment over the 6-month postoperative period. In other words, the presence of Tc-99m HMDP uptake is indicative of perioperative

Table 3 Serum creatinine and eGFR changes among 16 patients

		HMDP ⁻ (n=5)	HMDP ⁺ (n=11)	P value
sCr	Preoperative (mg/dl)	1.00±0.05	0.86±0.22	0.3079
	Postoperative 3 months (mg/dl)	1.03±0.05	0.95±0.23	0.6504
	Postoperative 6 months (mg/dl)	1.02±0.04	0.96±0.27 (n=10)	0.4624
	%change of sCr_postoperative 3 months (%)	3.9±5.4	12.3±10.2	0.0791
	%change of sCr_postoperative 6 months (%)	3.0±6.1	16.2±13.0 (n=10)	0.0864
eGFR	Preoperative (ml/min/1.73 m ²)	77.3±4.1	86.5±19.0 (n=9)	0.7389
	Postoperative 3 months (ml/min/1.73 m ²)	74.1±4.0	77.0±15.7 (n=10)	0.8065
	Postoperative 6 months (ml/min/1.73 m ²)	74.8±4.1	76.3±16.5 (n=10)	0.9512
	%change of eGFR_postoperative 3 months (%)	-4.1±5.8	-10.7±9.4 (n=9)	0.1615
	%change of eGFR_postoperative 6 months (%)	-3.1±6.3	-13.9±11.9 (n=8)	0.1073

Data are the mean ± standard deviation

eGFR, estimated glomerular filtration rate

sCr, serum creatinine

injury to innocent renal parenchyma, whereas the lack of Tc-99m HMDP uptake highlights the success of the minimally invasive procedure during NSS.

Regarding the evaluation of postoperative renal dysfunction, the use of Tc-99m DTPA GFR scintigraphy has tremendous advantages over other techniques [6, 7]. The operated kidneys as well as the contralateral kidneys could be efficiently evaluated regarding the perioperative GFR changes. One interesting finding of the present study was that compensatory hyperfunction of the contralateral kidneys was not as prevalent during partial nephrectomy as expected during total nephrectomy [15]. In fact, this issue of compensatory hyperfunction has never been thoroughly investigated in partial nephrectomy. Another noticeable finding of the present study was the quantitative relationship between Tc-99m HMDP uptake and GFR impairment. The greater the asymmetric uptake of Tc-99m HMDP in the operated kidney, the greater the percent change (functional deterioration) of the split GFR of the corresponding kidney. Therefore, Tc-99m HMDP uptake within 1 week post-NSS could play a role in predicting GFR decline 6 months thereafter. It is not clear whether there is a therapeutic option to prevent GFR impairment between the immediate postoperative period (at the time of bone scintigraphy) and 6 months thereafter, but awareness of

renal injury immediately after NSS could initiate other nephron-sparing efforts post-NSS. Finally, the limitations of traditional GFR markers, such as sCr or eGFR, were prominent compared with gamma camera imaging-based GFR measurement. For example, split and total GFR from Tc-99m DTPA scintigraphy were found to be significantly decreased in the HMDP⁺ operated kidneys over the 6-month post-NSS period (Table 2 and Fig. 4), but neither sCr nor eGFR revealed the change even in total GFR (Table 3). The high reliability and accuracy of the revised Gates' GFR scintigraphy technique was reported previously. We believe that Tc-99m DTPA GFR scintigraphy holds great promise for the measurement of perioperative GFR changes and could play a more significant role in renal function preservation during NSS.

Limitations

The retrospective nature of the study and relatively small number of enrolled cases restrict the clinical utility of the current findings. However, because baseline and postoperative Tc-99m DTPA GFR scintigraphy is routinely performed at regular intervals at our institution, we attest that patient selection bias was minimized. Furthermore, the proof of concept regarding the relationship between Tc-99m HMDP uptake and GFR decline is clear enough to drive future studies. We hope that a larger scale prospective study will lead to the development of a more effective nephron-sparing procedure using Tc-99m HMDP uptake as a surrogate marker of renal injury.

Conclusion

Tc-99m HMDP uptake within 1 week following nephron-sparing surgery is a surrogate marker of GFR impairment over 6 months post nephron-sparing surgery.

Acknowledgments We are grateful to Sang Eon Kim and Kyung Hoon Kim for their excellent technical assistance during Tc-99m DTPA GFR scintigraphy. This study was supported in part by a grant of the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (A111627-1101-0000100), and by grants from the National Research Foundation (NRF), Ministry of Education, Science and Technology (MEST), Republic of Korea (2012M2B2A9A02029612, 2014M2B2A9030104 and Basic Science Research Program 2012R1A1A2001060).

Ethical Statement This study was approved by our hospital's ethics committee (IRB no. = B-1310/224-103) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Obtaining patients' consent was waived by the ethics committee. Details that might disclose the identity of the subjects were omitted.

Conflict of Interests Hongyoon Choi, Won Woo Lee, Young So, Seunggyun Ha, Seok-Soo Byun, and Sang Eun Kim declare that there is no conflict of interest.

References

1. Ljungberg B, Hanbury DC, Kuczyk MA, Merseburger AS, Mulders PF, Patard JJ, et al. Renal cell carcinoma guideline. *Eur Urol*. 2007;51:1502–10.
2. Weight CJ, Larson BT, Fergany AF, Gao T, Lane BR, Campbell SC, et al. Nephrectomy induced chronic renal insufficiency is associated with increased risk of cardiovascular death and death from any cause in patients with localized cT1b renal masses. *J Urol*. 2010;183:1317–23.
3. Lane BR, Babineau DC, Poggio ED, Weight CJ, Larson BT, Gill IS, et al. Factors predicting renal functional outcome after partial nephrectomy. *J Urol*. 2008;180:2363–8. discussion 8–9.
4. Choi JD, Park JW, Choi JY, Kim HS, Jeong BC, Jeon SS, et al. Renal damage caused by warm ischaemia during laparoscopic and robot-assisted partial nephrectomy: an assessment using Tc 99m-DTPA glomerular filtration rate. *Eur Urol*. 2010;58:900–5.
5. Hakimi AA, Ghavamian R, Williams SK, Kim PH, Chen L, Sfakianos JP et al. Factors that affect proportional glomerular filtration rate after minimally invasive partial nephrectomy. *J Endourol*. 2013.
6. Becker F, Van Poppel H, Hakenberg OW, Stief C, Gill I, Guazzoni G, et al. Assessing the impact of ischaemia time during partial nephrectomy. *Eur Urol*. 2009;56:625–34.
7. Thompson RH, Lane BR, Lohse CM, Leibovich BC, Fergany A, Frank I, et al. Every minute counts when the renal hilum is clamped during partial nephrectomy. *Eur Urol*. 2010;58:340–5.
8. Peller PJ, Ho VB, Kransdorf MJ. Extraosseous Tc-99m MDP uptake: a pathophysiologic approach. *Radiographics*. 1993;13:715–34.
9. Demirel K, Sadic M, Korkmaz M, Comak A, Atilgan HI, Koca G. Diffuse myocardial uptake of 99mTc-HDP in multiple myeloma. *Nucl Med Mol Imaging*. 2013;47:208–11.
10. Buja LM, Tofe AJ, Kulkarni PV, Mukherjee A, Parkey RW, Francis MD, et al. Sites and mechanisms of localization of technetium-99m phosphorus radiopharmaceuticals in acute myocardial infarcts and other tissues. *J Clin Invest*. 1977;60:724–40.
11. McDougal WS. Renal perfusion/reperfusion injuries. *J Urol*. 1988;140:1325–30.
12. Lavelle KJ, Park HM, Moseman AM, Lewis S. Renal hyperconcentration of 99mTc-HEDP in experimental acute tubular necrosis. *Radiology*. 1979;131:491–5.
13. Thomsen HS, Taylor Jr A. Evaluation of renal ischemia with 99mTc-pyrophosphate. *Eur J Nucl Med*. 1982;7:147–9.
14. Inoue Y, Ohtake T, Kameyama S, Yamazaki S, Kawabe K, Yoshikawa K, et al. Increased renal retention of 99mTc-methylene diphosphonate after nephron-sparing surgery. *J Nucl Med*. 1999;40:418–21.
15. Kim YI, Ha S, So Y, Lee WW, Byun SS, Kim SE. Improved measurement of the glomerular filtration rate from Tc-99m DTPA scintigraphy in patients following nephrectomy. *Eur Radiol*. 2014;24:413–22.
16. Gates GF. Computation of glomerular filtration rate with Tc-99m DTPA: an in-house computer program. *J Nucl Med*. 1984;25:613–8.
17. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296–305.
18. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 2006;145:247–54.
19. Kim HO, Chae S-Y, Baek S, Moon DH. Factors affecting changes in the glomerular filtration rate after unilateral nephrectomy in living kidney donors and patients with renal disease. *Nucl Med Mol Imaging*. 2010;44:69–74.