The 3-D Volumetric Measurement Including Resected Specimen for Predicting Renal Function After Robot-assisted Partial Nephrectomy

Yosuke Mitsui, Takuya Sadahira, Motoo Araki, Yuki Maruyama, Shingo Nishimura, Koichiro Wada, Yasuyuki Kobayashi, Masami Watanabe, Toyohiko Watanabe, and Yasutomo Nasu

OBJECTIVE To investigate the relationship between postoperative renal function and resected cortex margin volume calculated by a 3-dimensional reconstruction technique based on the resected specimen, and to determine predictors of renal function after robot-assisted partial nephrectomy.

METHODS A total of 114 patients underwent robot-assisted partial nephrectomy from 2014 to 2018. Patients without a 1 mm slice computed tomography or renal scintigraphy were excluded. We identified the margins of the tumor from each resected specimen with 2 mm margin being added as the ischemic margin. The volume of the renal cortex was calculated automatically using 3-dimensional volume analyzer software. The total margin volume was excluded from the ipsilateral cortex volume to calculate the cortex volume split. Predicted estimated glomerular filtration rate (eGFR) was calculated using the change in cortex volume and then compared with the actual eGFR.

RESULTS Eighty-two patients were included in this retrospective study. Sixty-six patients (80%) were cT1a. A strong correlation was observed between renal scintigraphy split and pre- and postoperative cortex volume split (Pearson correlation coefficient $r = 0.9330$ and 0.8742, respectively). The predicted eGFR correlated strongly with post 1, 3, 6, and 12 months eGFR ($r = 0.8929$, 0.9294, 0.9320, and 0.8952, respectively). Preoperative relative renal function and total cortex margin volume were independent risk factors for decreasing postoperative renal function.

CONCLUSION This precise volumetric assessment that includes the resected margin is an alternative to renal scintigraphy for predicting postoperative relative renal function. The healthy cortex margin volume calculated by the reconstruction technique is an independent risk factor of decreasing postoperative renal function. UROLOGY 125: 104−110, 2019.

Robot-assisted partial nephrectomy (RAPN) is the standard treatment for minimally invasive nephron-sparing surgery for patients with a small renal cell carcinoma (RCC).[1,2] The oncologic outcomes of partial nephrectomy (PN) are equivalent to radical nephrectomy and superior for preserving renal function.[3,4]

A technetium-99m mercapto acetyltriglycin (MAG3) scan is used widely to evaluate relative split renal function (SRF) after PN.[5,6] Recently, renal volumetric assessment using computed tomography (CT) has become a well-established alternative to MAG3 scan for evaluating SRF in radical nephrectomy.[8-10] Although several studies have reported an association between loss in renal volume and SRF in PN, no standardized methods for the measurement of a resected healthy margin have been fully defined.[11-15]

A renal hilar clamp is employed frequently to achieve a bloodless surgical field during a RAPN. Many studies have reported that the duration of warm ischemic time (WIT) could be a risk factor for renal damage.[11,14,15] A recent study showed that preservation of renal cortex volume was a strong predictor of postoperative renal function.[16] This association occurred because renal cortex volume is correlated with nephron mass. We consider that a precise technique for measuring resected cortex volume is needed to evaluate postoperative renal function.

The aim of this study was to investigate whether 3-dimensional volumetric measurement including the resected cortex margin accurately predicted SRF, and to

Financial Disclosure: *The authors declare that they have no relevant financial interests.*
From the Department of Urology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1, Shikata-cho, Kita-ku, Okayama, 700-8558, Japan

Address correspondence to: Takuya Sadahira M.D., Ph.D., Department of Urology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1, Shikata-cho, Kita-ku, Okayama 700-8558, Japan.

E-mail: t.sadahira@gmail.com
Submitted: November 9, 2018, accepted (with revisions): December 17, 2018

https://doi.org/10.1016/j.urology.2018.12.020
0090-4295

determine the factors that predicted renal function after RAPN.

MATERIALS AND METHODS

Patients

We retrospectively identified 114 patients with RCC who had undergone RAPN between 2014 and 2018 at our institution. The exclusion criteria for the study are shown in Supplementary fig. 1.

CT and MAG3 Scan Protocol

A CT scan was performed using a 64-slice multidetector CT scanner (Toshiba Medical Systems Corporation, Tochigi, Japan), with all patients having a 1 mm slice contrast enhanced-CT before RAPN. All patients in the study had a MAG3 scan 3-8 months after the RAPN.

The Measurement of Tumor Margin and Renal Cortex Volume

The resected specimen was cut through the middle of the tumor. We took a picture of the tumor with a ruler. We identified the margins of the tumor in each resected specimen and defined the margin as the mean between the widest and narrowest point from ruler (Fig. 1A, C, and Supplementary fig. 2). We also defined the ischemic margin; 2 mm as electrocoagulation or renorrhaphy. The volume of the renal cortex was calculated automatically using 3-D volume analyzer software (Synapse Vincent ver. 4, Fujifilm, Tokyo, Japan). Fig. 1B and D show the volumes of the renal cortex (blue), tumor (red), and margin of the tumor (yellow). The total margin volume including the ischemic margin was excluded from the volume of the ipsilateral cortex.

Formula for Calculating Predicted eGFR

Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[17] We predicted postoperative renal function using the change in renal cortex volume as follows: predicted renal function = SRF in the nontumor bearing kidney + SRF in the tumor-bearing kidney × (cortex volume in the tumor-bearing kidney − margin cortex volume of tumor/cortex volume in the tumor-bearing kidney) (Supplementary fig. 2).

Statistical Analysis

The correlation between MAG3 and cortex volume in the tumor-bearing kidney was evaluated using the Pearson correlation coefficient and Bland-Altman plots, a graphical method for comparing 2 measurements. In this method, the differences between the 2 measurements are plotted on the y-axis and the means of the 2 techniques on the x-axis. The Pearson correlation coefficient was used to measure the strength of the linear association between postoperative eGFR at 1, 3, 6, and 12 months and predicted eGFR measured by cortex volumetry. Simple and multiple linear regression analyses were used to determine the factors that contributed to the deviation between MAG3 split and cortex volume split after RAPN. Statistical significance was set at P <.05 for all analyses. All the statistical analyses were performed using JMP 13.2 software (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics and Volumetric Status

Eighty-two patients were included in this retrospective study. Supplementary table 1 shows the characteristics of the patients.

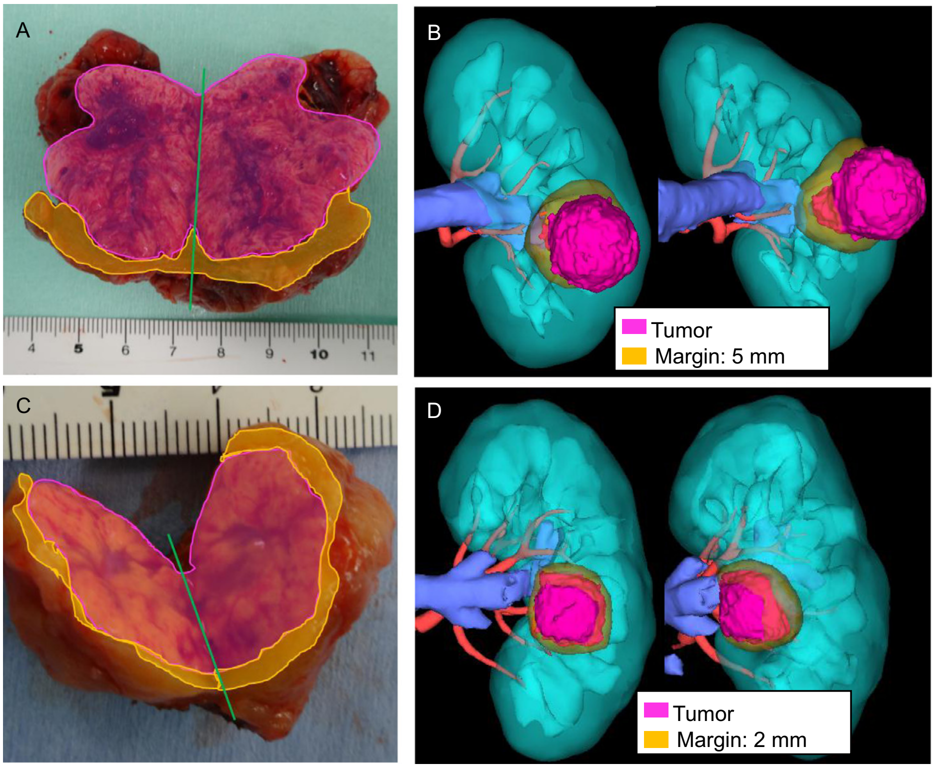

Figure 1. Three-dimensional volumetry of the tumor-bearing kidney and resected specimen. (Color version available online.)

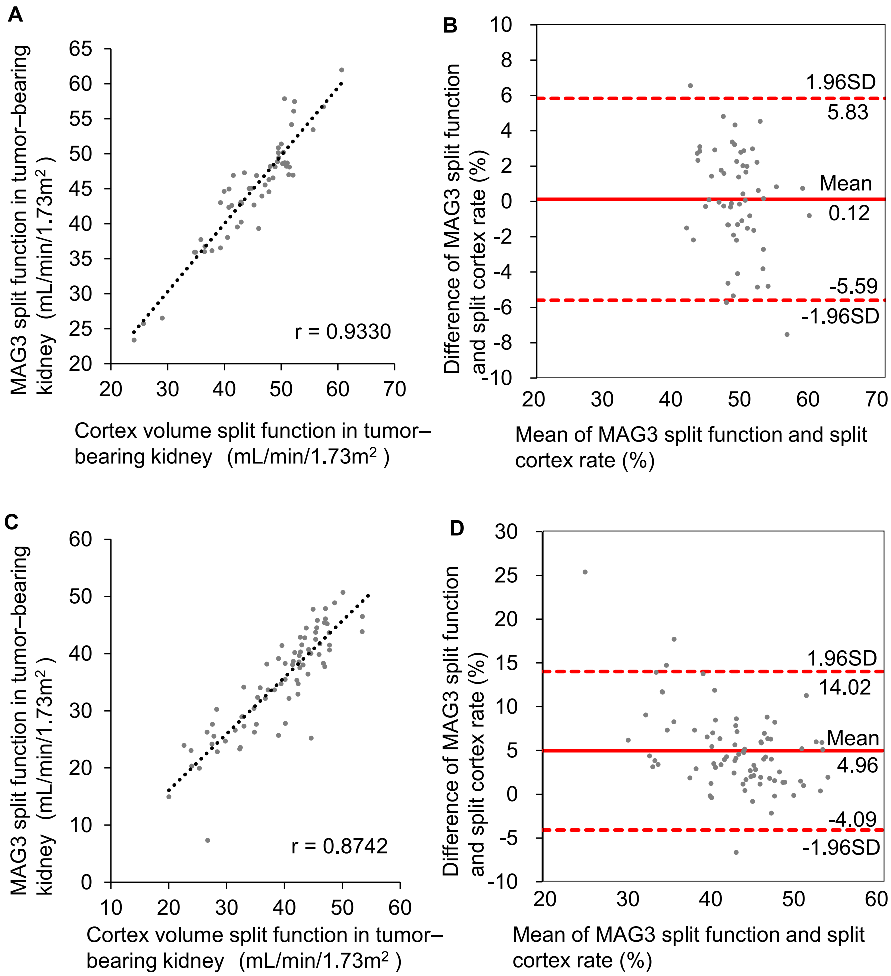

Figure 2. (**A and B**) Correlation between preoperative MAG3 split and renal cortex volume split in the tumor-bearing kidney (n = 55). (**C and D**) Correlation between postoperative MAG3 split and renal cortex volume split in the tumor-bearing kidney (n = 82). (Color version available online.)

The median age was 60 (29-83) year, and 53 patients (65%) were male. In R.E.N.A.L. nephrometry score, 25 patients (31%) were low score and 56 patients (68%) were medium score and 1 patient (1%) was high score. The median of tumor size was 2.6 (1-5.1) cm. Sixty-six patients (80%) ware cT1a and 16 patients (20%) were cT1b. Supplementary table 2 shows pre- and postoperative renal function and 3-D volumetric status measured by CT. A total of 10% (-35.5 to 3.9%) had decreased relative renal function in the tumor-bearing kidney after RAPN. The median margin identified from the resected specimens was 5 (2-11) mm. The median of the cortex volume excluded from the ipsilateral kidney is 14.6 (3.8-55.7) mL. Supplementary table 3 shows the results of the operation and the histopathological findings. Median operation time was 180 (90-400) minute, bleeding volume was 32.5 (10-850) mL, and ischemic time was 10 (7.5-63) minute. Sixty-nine patients (84%) were diagnosed as having a clear cell carcinoma.

Correlation Between Cortex Volumetry and MAG3 in pre-/post-RAPN

Fig. 2A and C show the strong correlation between MAG3 split and cortex volume split in the tumor-bearing kidney before and after RAPN. The correlation coefficients r were 0.9330 and 0.8742, respectively. The Bland-Altman plots with the mean differences between the 2 measurements are shown in Fig. 2B and D.

Correlation Between Predicted eGFR and Actual eGFR After RAPN

Fig. 3 shows the correlation between predicted eGFR measured by cortex volumetry and postoperative eGFR at 1, 3, 6, and 12 months. The correlation coefficients r were 0.8929, 0.9294, 0.9320, and 0.8952, respectively.

Simple and Multiple Liner Regression Analysis

Simple linear regression analysis showed that preoperative renal function in the tumor-bearing kidney, bleeding volume, WIT, and total margin volume correlated significantly with the deviation between MAG3 SRF and cortex volume SRF after RAPN. These 4 variables were then analyzed by multiple linear regression. Preoperative renal function in the tumor bearing kidney and total margin volume were shown to be independent risk factors for decreasing relative renal function after RAPN (Table 1).

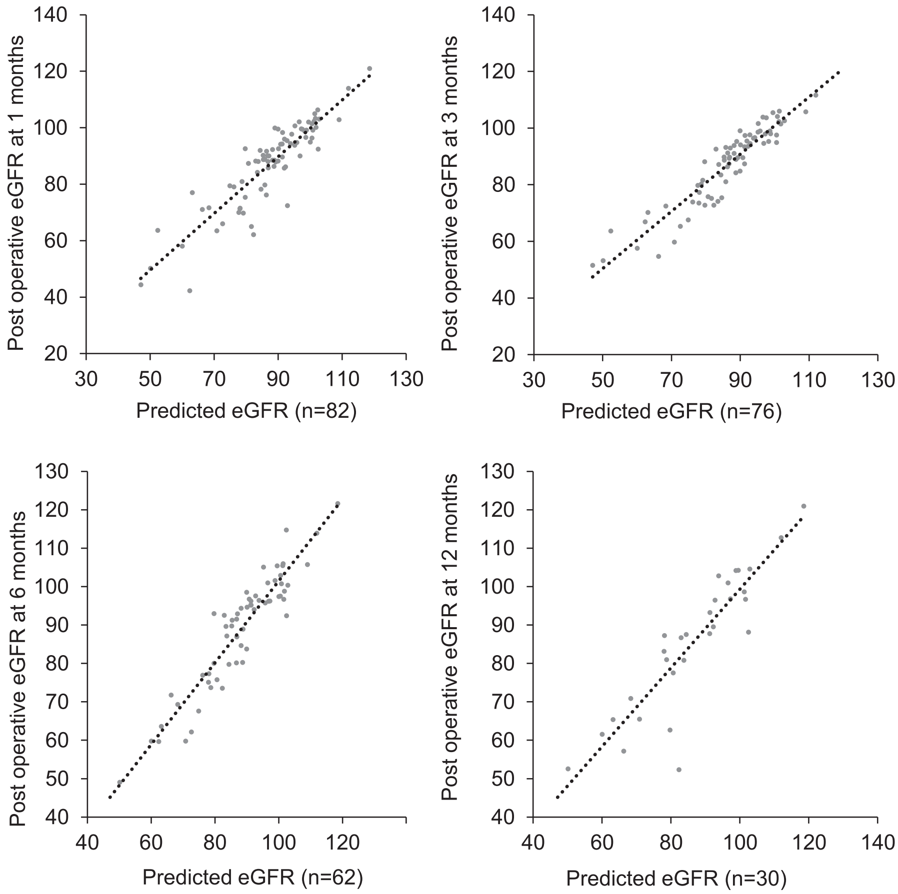

Figure 3. Correlation between predicted eGFR from volumetry and postoperative eGFR at 1, 3, 6, and 12 months.

Table 1. Simple and multiple linear regression analysis of risk factors associated with decreasing split renal function compared with predicted split renal function measured by cortex volumetry

Variables	Univariate			Multivariate		
	Coefficient	(95 % CI)	*P* value	Coefficient	(95% CI)	*P* value
Age	0.067	(−0.027, 0.159)	.159			
Gender (male)	−0.123	(−1.148, 0.903)	.812			
Body mass index	0.001	(−0.271, 0.273)	.994			
Drinker	−0.231	(−1.214, 0.753)	.753			
Smoker	−0.583	(−1.573,0.407)	.244			
Hypertension	−0.583	(−1.067, 0.903)	.869			
Diabetes mellitus	−1.172	(−2.490, 0.147)	.081			
HbA1c	0.362	(−1.284, 2.009)	.662			
Pre-eGFR split in tumor-bearing kidney	−0.128	(−0.267, −0.065)	.007	−0.135	(−0.262,−0.008)	.038
R.E.N.A.L. score						
Total score	0.235	(−0.401, 0.871)	.464			
PADUA score						
Total score	−0.091	(−0.794, 0.612)	.797			
Operation data						
Operation time	−0.012	(−0.030, 0.006)	.186			
Estimated blood loss	−0.012	(−0.018, −0.005)	.001	−0.008	(0.018,0.001)	.078
Warm ischemic time	−0.110	(−0.203, −0.017)	.021	0.052	(−0.076, 0.180)	.419
Hospitalization time after surgery	0.165	(−0.415, 0.745)	.752			
Total margin volume	−0.176	(−0.273, −0.079)	<.001	−0.138	(−0.266.−0.009)	.037
Tumor volume	−0.017	(−0.085, −0.052)	.630			

DISCUSSION

The present study demonstrated that 3-D cortex volumetry by CT was effective for evaluating SRF in both pre- and post-RAPN. Using the measurements of the margins of the tumor from the resected specimens and reconstructed 3-D imaging we showed there was a close correlation between cortex volume and MAG3, and that we were more able to accurately predict postoperative renal function. This 3-D volumetric technique predicted SRF precisely and was reproducible. In addition, we showed that the volume of the resected healthy cortex margin was the most significant predictor of the decrease in postoperative renal function.

Several studies have reported a correlation between renal scintigraphy and renal cortex volume in radical nephrectomy.[8-10,18,19] For example, there is evidence of a strong correlation between cortex volume and MAG3 in donor nephrectomy, with the correlation coefficient r ranging between 0.82 and 0.92.[8-10] Our study showed a strong correlation between the 2 methods in pre- and post-RAPN ($r = 0.9330$ and 0.8742, respectively). The level of correlation was stand comparison with donor nephrectomy, nevertheless our subjects were tumor-bearing patients with underlying diseases, as 43% of the patients were hypertensive and 13% had diabetes mellitus. Despite differences in the patient's backgrounds, the cortex volume correlated strongly with the MAG3 scan.

A method for measuring the healthy margin of the resected tumor has not been fully defined, and has varied between different studies. Some studies used fixed values for the resected margin in all patients,[13,20] while other studies calculated the resected margin using ellipsoid methods.[11,15] The novel and innovative method used in the present study was a 3-D CT reconstruction technique. By identifying the actual margin from the resected specimen we were able to accurately measure the margin volume in each patient. In general, renal scintigraphy was performed to evaluate SRF after PN and increased both the patient's burden for radiation exposure and examination costs.[7-10] The volumetric methods effectively reduced both these burdens. Our 3-D CT reconstruction technique of the resected specimen has a major advantage, in that all patients routinely have a CT performed before RAPN to evaluate the tumor and vasculature and therefore do not require an extra examination after RAPN. The strength of this study is that it is simple and easy just using preoperative CT.

Several studies have reported the risk factors for the degree of renal function loss after PN, which included WIT, tumor size, nephrometry score, preoperative eGFR, and estimated blood loss.[5,6,11-15] Although the effect of tumor size, nephrometry score, and estimated blood loss on functional outcome have differed in these studies, WIT is widely regarded as a significant factor that affects renal function after PN. Only a few studies analyzed either the resected margin or preserved cortex volume with WIT to determine postoperative renal function.[11,14,15] Thompson et al suggested that the effect of ischemia was not important regardless of ischemic time, but that preservation of the renal parenchyma was the main predictor of postoperative renal function.[21] Choi et al and Zargar et al reported that the volume of resected healthy tissue and WIT predicted functional outcome, with both papers suggesting preservation of renal volume was a more precise assessment tool of renal function after PN.[11,15] Our study showed that preoperative renal function in the tumor-bearing kidney and total margin volume were independent risk factors for decreased SRF after RAPN. There is evidence that WIT in RAPN was shorter compared to that in laparoscopic PN because of robotic assistance, and was not identified as a predictor for functional outcome.[22] Our reconstruction technique was able to measure cortex healthy margin more precisely than the ellipsoid method. Moreover, all patients included in our study underwent a 1 mm slice CT, with the slice interval being an important factor for constructing the 3-D image and accurately measuring renal volume.

Previous studies have suggested that preserved renal parenchymal volume was a predictor of renal function after PN.[11-15] However, we measured and evaluated renal cortex volume in this study because it has been reported that renal cortex volume correlates with nephron mass and total functional glomerular number.[23] Several studies reported a correlation between renal cortex volume and renal function in radical nephrectomy.[8-10] Almost all patients in our study were classified as clinical T1a stage and had an exophytic mass. We considered that the resected healthy margin included more cortex component than renal medulla and accordingly selected the volume of the renal cortex to evaluate renal function. We also investigated the correlation between renal parenchymal volume and renal function after RAPN using the same methods (Supplementary fig. 3). Our data showed the correlation between the parenchyma and SRF is comparable to the result for cortex. No other studies have calculated both cortex and the parenchyma in PN.

Recent study reports that several methods of predicting postoperative eGFR have accuracy about 90%, due to strong anchoring to preoperative eGFR.[24] Our results suggest preoperative eGFR and resected healthy cortex volume based on resected tumor are the factors of decreasing postoperative eGFR. This is because there is the correlation between resected healthy margin volume and decreased eGFR ($r = 0.4644$-0.5963) (Supplementary fig. 4). This report includes less than 5.0 cm of tumor, and 60% of cT1a, while our study includes less than 5.1 cm of tumor, and 80% of cT1a. We think that validation with larger tumors is expected to confirm the results shown in the present study.

The present study had several limitations. First, it was a retrospective study carried out at a single institution, and the sample size was relatively small. Second, 3-D volume analyzer software requires thin slice CT of at least 2 mm in order to measure renal volume accurately. We routinely perform CT using 5 mm intervals after RAPN to confirm whether or not there is a recurrence and metastasis. Therefore, we cannot compare changes in CT volume before and after RAPN. Third, the choice of a 2 mm ischemic margin was based on our experience. Some reports have shown that a 5 mm total of normal parenchyma excludes as healthy lesion. These margins included the additional tissue damaged by renorrhaphy.[13,20] And, the depth of necrosis by soft coagulation is 1.2 mm per 3 seconds and 2.3 mm per 6 seconds. We usually use soft coagulation less than 3 seconds. Therefore, we considered it was appropriate to use a 2 mm extra margin in our study. Fourth, 80% of the patients (66/82) were cT1a, and 20% were cT1b (16/82). Although 38% (31/82) of PADUA score is high, RENAL nephrometry score is low in 31% (25/82) and medium in 68% (56/82). Therefore, the complexity may present all incoming PN candidates but size of the tumors was relatively small. Further validation is required especially for larger tumors. Although the present study focused on the usefulness of 3-D volumetric methods for predicting postoperative split renal function, we also showed the clinicopathological factors associated with reducing the renal cortex after RAPN are important. We do believe further study with larger tumors is expected to clarify the point in the near future. Finally, we did not consider the influence of compensatory hypertrophy in our study. Previous studies have reported a 10%-20% increase in contralateral parenchymal volume after radical nephrectomy.[25,26] Compensatory hypertrophy should therefore be taken into account in PN. Another earlier study reported an approximate 5% increase in contralateral kidney parenchymal volume.[27] However, these studies investigated open or laparoscopic PN. In our study, all patients underwent a RAPN that resulted in better preservation of parenchymal volume than that achieved by a PN.[28] We assume that the increased rate of contralateral renal volume that occurs with compensatory hypertrophy may be less than 5%.

Despite these limitations, the current study demonstrated that the 3-D reconstruction method just using preoperative CT including the resected cortex margin volume easily and objectively evaluated SRF and predicted postoperative renal function. Moreover, the volume of the cortex margin calculated precisely by this technique was an independent risk factor of functional outcome.

CONCLUSION

Volumetric assessment using CT is an alternative to MAG3 for evaluating SRF and predicting postoperative renal function in patients with a RCC. By measuring individual margins in resected specimens, we were able to more precisely predict renal function. Our study suggested that the operator in nephron sparing surgery should carry out a careful resection of the tumor in order to preserve the volume of the cortex as much as possible.

ETHICS

The clinical study was approved by the Okayama University Institutional Review Board prior to initiation of the study (Registration no.1810-011).

Acknowledgments. The authors thank the clinical laboratory technicians of Okayama University Hospital for their technical support.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.urology.2018.12.020.

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