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The significance of predictable traumatic area by renorrhaphy in the prediction of postoperative ipsilateral renal function

Toshihiko Masago[1,2], Noriya Yamaguchi[1], Hideto Iwamoto[1], Shuichi Morizane[1], Katsuya Hikita[1], Masashi Honda[1], Takehiro Sejima[3], Atsushi Takenaka[1]

[1]*Division of Urology, Department of Surgery, Tottori University Faculty of Medicine, Tottori, Japan*
[2]*Division of Urology, Department of Surgery, National Hospital Organization, Yonago Medical Center, Tottori, Japan*
[3]*Division of Urology, Matsue City Hospital, Shimane, Japan*

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Corresponding author
Toshihiko Masago
Tottori University
Faculty of Medicine
Division of Urology
Department of Surgery
36-1 Nishi-cho, Yonago
Tottori 683-8504, Japan
phone: +81 859 38 6607
masago0120@gmail.com

Introduction To determine the relationship between the actual renal function loss and volume loss in robot-assisted partial nephrectomy (RAPN) using a novel three-dimensional volume analyzer.

Material and methods We respectively evaluated the medical records of 23 consecutive patients who underwent RAPN between January 2012 and March 2016 and the data on their kidney function and parenchymal mass specific to the operated kidney. Parenchymal volume was measured by computerized tomography and reconstructed with a Synapse Vincent volumetric analyzer. Using this system, we predicted the renal vascular territory and other trauma areas involved in renorrhaphy. All measurements were taken within 3 and 6 months pre- and postoperatively, respectively.

Results The actual postoperative renal parenchymal volume was significantly correlated with the virtual predicted residual renal volume excluding the tumor and resected margin (r = 0.435, p <0.05). The ratio of split estimated glomerular filtration rate (eGFR) postoperative/preoperative) was significantly correlated with the virtual predicted residual renal volume excluding the resected margin and the traumatic area by renorrhaphy (r = 0.401, p <0.05).

Conclusions When predicting the reduction of renal function of the diseased side following partial nephrectomy, adding the extent of the area traumatized by renorrhaphy might be useful for predicting the postoperative split renal function of the affected kidney.

Key Words: robot-assisted partial nephrectomy ‹› traumatic region ‹› virtual system

INTRODUCTION

If technically feasible, partial nephrectomy (PN) is the standard treatment for small renal masses (clinical stage T1a). The oncologic outcomes of PNs are equivalent to those of radical nephrectomy, but with a better preservation of renal function [1]. In renal cell carcinoma (RCC), nephrectomy improves oncologic outcome, but the loss of a large amount of nephron tissue predisposes patients to progress to chronic kidney disease and was associated with increased cardiovascular disease morbidity and decreased survival [2]. The objective of a PN is to preserve as much renal function as possible while achieving negative surgical margins, all within the context of a low perioperative complication rate [3–5]. The results of several studies have shown that the quality of the preserved parenchymal mass is the best predictor of renal function after PN [6–9].

Achieving the best PN outcomes requires the use of the open, laparoscopic, or robot-assisted approaches that are selected based on individual tumor characteristics, the surgeon's experience and institution-related factors. Renorrhaphy is a very important technique for achieving

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adequate hemostasis and reconstruction of the kidney within a reasonable warm ischemic time during a PN. However, the renorrhaphy technique may cause an injury to renal arterial branching and affect the peripheral blood flow, and an irreversible ischemic alteration of residual renal parenchyma could occur. To the best of our knowledge, there has been no study that considered the influence of renal function after renorrhaphy conducted during a PN. We hypothesized that the renal function of the affected kidney would be damaged because of regions that were traumatized by renorrhaphy, whereas the total residual renal function would not change markedly [10, 11, 12]. To investigate the influence of traumatized regions, we evaluated the impact of patient operative and tumor characteristics on the degree of renal volume preservation. We also performed a formal volumetric analysis with the aid of three-dimensional (3D) rendering software to accurately measure the residual renal volume.

MATERIAL AND METHODS

Patient population

The 40 consecutive patients who underwent robot-assisted partial nephrectomy (RAPN) surgery including a 3D volume analyzer and nuclear renal scans at our institution between January 2012 and March 2016 were eligible for this study. Thirteen patients could not undergo enhanced computed tomography (CT) postoperatively and four patients did not appear for the postoperative mercapto-acetyltriglycine (MAG3) renal scan. Seventeen patients without available imaging data or who were not suitable for the 3D volume analysis and renal scans were excluded. The clinical features of the patients are summarized in Table 1. Each patient's renal function was monitored preoperatively by determining the patient's creatinine level and estimated glomerular filtration rate (eGFR) and by performing a renal scan. All patients gave their informed consent to participate in the study, and the study design was approved by the institutional Research Ethics Committee of Tottori University (No. 2692).

Process of virtual resection of renal parenchyma using 3D simulation software

The CT images were manipulated with a Synapse Vincent volumetric analysis system ver. 4 (Fujifilm, Tokyo), an image-processing software package dedicated to DICOM images.

Table 1. *Patient characteristics*

Mean age, years (IQR)	60.4 (39–87)
No. of males (%)	13 (56)
No. of females (%)	10 (44)
Mean BMI, kg/m^2 (IQR)	23.7 (19–31.2)
CCI (%)	
2 or less	11 (49)
3–4	11 (49)
5 or more	1 (2)
Tumor laterality (%)	
Right	10 (44)
Left	13 (56)
Mean tumor size, cm (IQR)	2.0 (1.2–4.5)
Tumor complexity (%)	
Low (R.E.N.A.L score, 4–6)	9 (39)
Intermediate (R.E.N.A.L score, 7–9)	12 (52)
High (R.E.N.A.L score, 10–12)	2 (9)

IQR – Interquartile Range; R.E.N.A.L – Radius, Exophytic/endophytic tumor properties, Nearness of tumor deepest portion to collecting system or sinus, Anterior/posterior and Location relative to polar line; CCI – Charlson Comorbidity Index

1. Extraction of renal tumor and area of renorrhaphy and renal artery
The 23 patients were preoperatively evaluated using enhanced 1.0-mm thin-slice CT images (Figure 1A). The renal parenchyma was semi-automatically extracted from consecutive CT images (Figure 1B). We set the predicted excision volume after presuming a loss of a 5-mm rim of normal parenchyma-related excision and renorrhaphy. The renal structures were extracted. With this image processing process, a semi-automatic extraction of the renal tumor, areas of renorrhaphy, and the renal artery was achieved (Figure 1B,C). In all instances, the renal sinus fat, collecting system, and non-enhancing cysts were excluded from the analysis as they were non-vascularized parenchyma.

2. The identification of the renal branch involved in the renorrhaphy
The 3D reconstruction system that we used enabled confirmation of the virtual residual renal parenchyma separate from the renal tumor and resected margin and the area of renorrhaphy (Figure 1D). The renal arterial branches involved in the renorrhaphy were then identified (Figure 1D,E).

3. Prediction of the renal vascular supplied territories
This system enabled the prediction of the renal vascular supplied area of a selected arterial branch based on Voronoi decomposition, a Euclidean distance met-

ric method [13, 14]. The sensitivity and specificity of this system were 100% (95%CI: 70.1–100%) and 72.5%, respectively [15]. With the new computational 3D analysis, the territories belonging to the selected arterial branch are presented in 2D images and in a color-coded 3D model (Figure 1F). Therefore, we were able to confirm the irreversible ischemic areas of renal arterial branches involved in the renorrhaphy.

Renal function evaluation

The decision to conduct a mercapto-acetyltriglycine (MAG3) renal scan was at the discretion of the treating physicians. The proportion of contribution toward total function was considered an indicator of the functional ability of the operated kidney. All serum creatinine measurements were made at a single clinical reference laboratory. The eGFR was estimated by the Modification of Diet in Renal Disease (MDRD) equation, adapted for a Japanese population. We defined preservation of the eGFR in the kidney of the patients who had undergone surgery as the ratio of the postoperative eGFR for the operated kidney to the preoperative eGFR for the operated kidney. Total eGFR preservation was calculated in the same manner (postoperative eGFR/preoperative eGFR × 100). All measurements were obtained in less than 3 and 6 months pre- and postoperatively, respectively.

Operation

In the present patient series, a single surgeon performed each RAPN. The surgical approach was

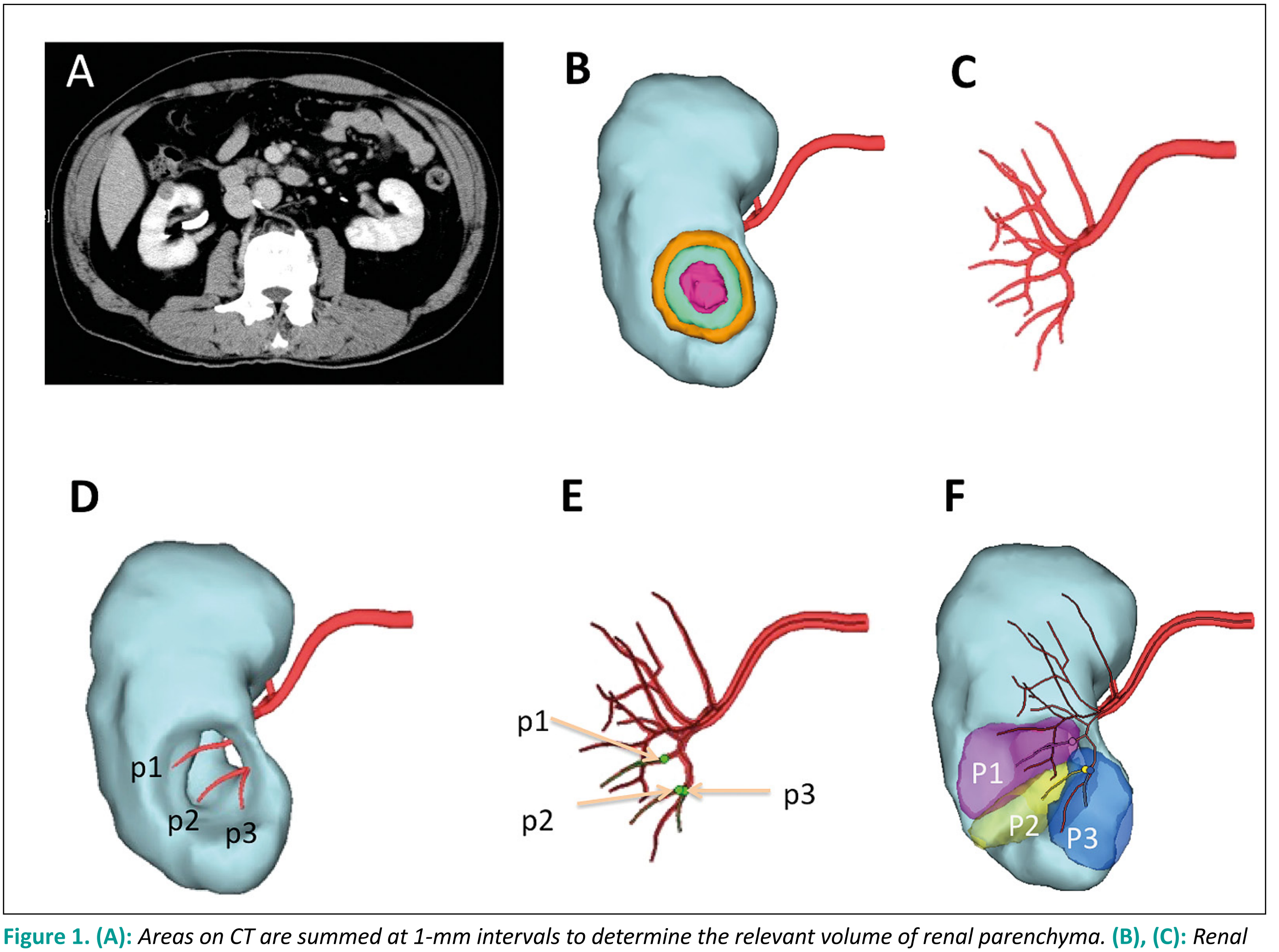

Figure 1. (A): *Areas on CT are summed at 1-mm intervals to determine the relevant volume of renal parenchyma.* **(B), (C):** *Renal parenchyma, renal tumor (red), resected margins (light blue), and areas of renorrhaphy (orange) were automatically reconstructed and extracted.* **(D):** *The removal of the target volume from normal parenchyma was permitted and then confirmed the resected section.* **(E):** *Electively, the branch of renal artery (such as p1, p2, or p3) was extracted after the removal of tumor, surgical margins, and renorrhaphy.* **(F):** *The vascular territories of p1, p2, and p3 were described.*

selected based on the position of the renal tumor Posterior tumors were treated retroperitoneally and anterior tumors were treated intraperitoneally. With both approaches, only the renal main artery was clamped in all cases. Each renal tumor was resected with a 5-mm margin of normal renal parenchyma, and was stitched closed with 3-0 V-Loc® thread at a 5-mm distance in a two-layer suture. Early unclamping of the main renal artery was not attempted.

Data analysis

Areas of interest were summed to yield the preoperative total volume of functioning renal parenchyma. We defined the irreversible traumatic region as the area of renorrhaphy plus the vascular area of the renal arterial branches involved in the renorrhaphy. The preoperative functional renal parenchyma and tumor were reconstructed (Figure 2A). The renal cortical volume of the entire kidney was automatically calculated by the summation of the cortical volumes in all slices in the arterial phase. The renal tumor and a 5-mm rim of surgical margin removed from the preoperative renal parenchyma were extracted in the virtual simulation (Figure 2B). The area of renorrhaphy and the predicted irreversible traumatic region were also removed in the virtual simulation (Figure 2C). The actual postoperative renal parenchyma was calculated and reconstructed (Figure 2D).

We then categorized the three types of residual renal parenchyma by changing patterns to determine the correlation between the actual renal parenchymal and the virtual renal parenchymal rate changes from the kidney that had undergone the RAPN. We calculated the renal parenchymal preservation of the kidney that had undergone the surgery as follows: (postoperative residual renal parenchyma)/(preoperative renal parenchyma ×100). We first compared the changes in the actual and virtual renal volumes, and then compared the change in the actual residual renal function with the renal residual volume change. In this process, we categorized the patients' residual renal volume ratio into three categories: I, II, III. All three categories reflected the virtual percentage change in renal volume. Category I = (actual postoperative renal volume)/(preoperative renal volume). Category II = [(preoperative renal volume) – (predicted volume of the virtual resection lesion)]/(preoperative renal volume). Category III = [(preoperative renal volume) – (predicted volume of the virtual resection lesion) – (predicted volume of the virtual traumatic lesion)]/(preoperative renal volume). Categories I, II, and III showed D/A, B/A, and C/A in the same manner.

We confirmed the correlation between the renal volume rate change in each category and the ratio of renal functional rate change in the kidney that had undergone surgery. The variables evaluated in each patient included age, gender, body mass index (BMI), Charlson Comorbidity Index (CCI), RNS (R.E.N.A.L. score), and % virtual volume change rate.

Statistical analysis

The results are presented as means and interquartile (IQR) range. The correlations are expressed

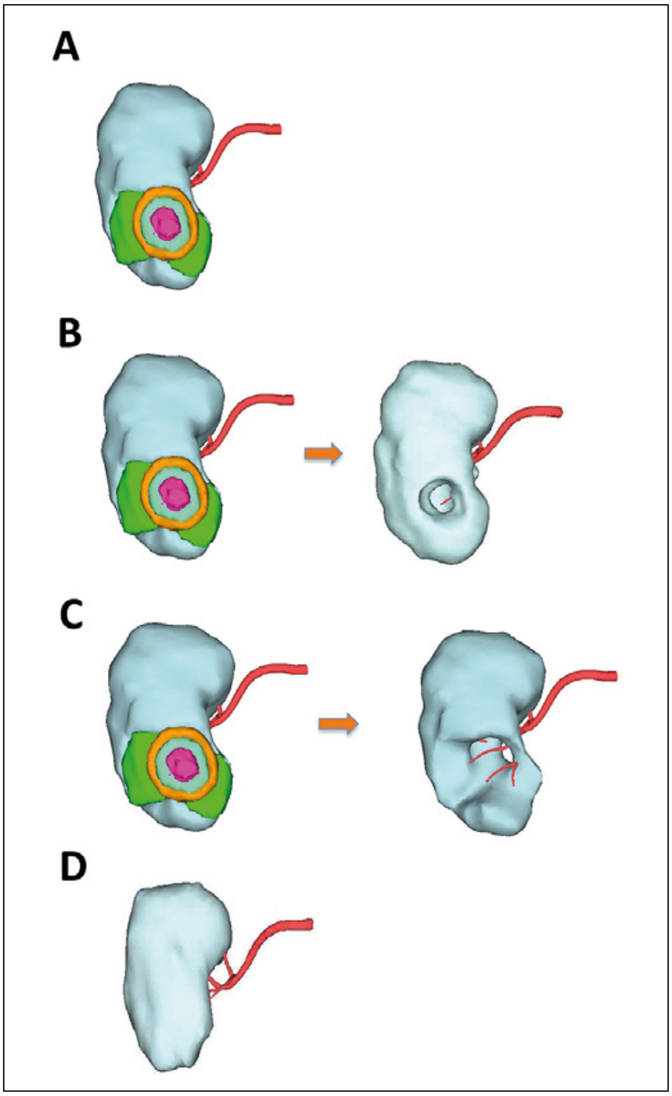

Figure 2. (A): *preoperative renal parenchyma including renal tumor (red), resected margin (light blue), the area of renorrhaphy (orange), and vascular territory (right green);* **(B):** *virtual surgical margin removed from preoperative renal parenchyma;* **(C):** *virtual surgical margin and predicted irreversible ischemic territory removed from preoperative renal parenchyma;* **(D):** *actual postoperative renal parenchyma.*

as scatter plots and were tested for significance by the Pearson correlation coefficient. The chi-square or Kruskal-Wallis test as appropriate was used for univariate comparisons. Multivariate linear regression models were used to identify variables that were independently related to a decrease in global kidney function. Linear regression assumptions were tested and met. The statistical analysis was performed with SPSS version 8 software (SPSS, Chicago, IL). P-values <0.05 were considered significant.

RESULTS

Patient population

The mean tumor size among the 23 patients was 2.2 cm (IQR, 1.2–4.5 cm). Two patients (9%) had a high-complexity tumor (R.E.N.A.L. score 10–12). Table 2 provides the parenchymal volumes and renal function characteristics of the affected kidneys. We calculated the eGFR of the kidneys after surgery

Table 2. *Parenchymal volume and renal function*

Mean operated kidney, ml (IQR)	Parenchymal volume
Actual resected volume	14 (5–50)
Virtual resected volume including tumor and resected margin	17.9 (6–52)
Virtual traumatic area	41.1 (8.8–89.5)
Actual pre-renal parenchymal volume	132.4 (85.6–240)
Actual post-renal parenchymal volume	120 (79.8–231.1)
Virtual residual volume removed from resected volume	112 (81.3–227.3)
Virtual residual volume removed from resected and traumatic area	87.9 (53.1–165)
% Parenchymal volume change (Actual Post/Pre)	85.3 (67.6–98.3)
% Parenchymal preservation rate (Virtual residual volume removed from resected volume/Pre)	89.4 (76.1–98.4)
% Parenchymal preservation rate (Virtual residual volume removed from resected and traumatic area/Pre)	63.2 (40.1–89.7)
Mean operated kidney, ml/min/1.73 m² (IQR)	**Renal function**
Preoperative eGFR	33.9 (19.3–54.1)
Postoperative eGFR	23 (12.0–43.3)
% GFR change (postoperative eGFR / preoperative eGFR)	33.7
Mean global, ml/min/1.73 m² (IQR)	**Renal function**
Preoperative eGFR	60.1 (41.6–104.0)
Postoperative eGFR	61.3 (33.3–105)
% GFR change (postoperative eGFR / preoperative eGFR)	7.9

IQR – Interquartile Range; eGFR – Estimated Glomerular Filtration Rate

by split renal function. The mean preoperative eGFR was 33.9 ml/min/1.73 m² (IQR, 19.3–54.1), and the mean postoperative eGFR was 23 ml/min/1.73 m² (IQR, 12.0–43.3). The mean postoperative eGFR was 66.3% of the preoperative values.

Correlation between renal functional preservation and renal parenchymal preservation

The virtual resected volume, including the tumor and resected margin, was correlated with the actual resected volume ($r = 0.445$, $p < 0.01$) (Figure 3A). When we compared the percentage change in parenchymal volume, we found that the mean residual renal volumes were 85.3% (IQR, 67.6–98.3) in Category I, 89.4% (IQR, 76.1–98.4) in Category II, and 63.2% (IQR, 40.1–89.7) in Category III. The change in Category I was significantly correlated with that in Category II ($r = 0.435$, $p < 0.05$) (Figure 3B), but not with the change in Category III ($r = 0.311$, $p = 0.159$, Figure 3B).
The mean change in eGFR was 33.7%. Our comparison of the percentage change in parenchymal volume with kidney function revealed that the change in the eGFR was significantly correlated with the category III change, and the relationship was stronger than those seen with categories I and II ($r = 0.401$, $p < 0.05$, Figure 3C). The effect of the observed changes in renal volume suggests not only that the influence of the ischemic area might be overestimated, but also that the percentage change in volume might be a more accurate indicator of the residual renal function. These results showed that virtual renal residual functional damage would be more severe than the postoperative residual renal volume at the operated kidney.

DISCUSSION

The preservation of renal function is an important goal of PN. Several modifiable factors potentially impact renal function after PN. The control of technical variables such as minimizing the ischemia time (ideally having zero ischemia) and super-selective clamping is important for preserving kidney function [16–20]. Before PN surgery, it is important to understand the vascular area and to calculate the renal vessel territories accurately. In the present study patients, a Synapse Vincent volumetric analysis system was used; this system was reported as a beneficial tool for acquiring quantitative 3D RAPN simulation [15]. Many 3D simulation software packages enable the estimation of renal preservation by a detailed surgical process with computational methods [12, 17, 21]. To our knowledge, the Synapse Vincent is the only tool capable of confirming the bottom of a resected margin and the vascular territories of renal vessels.

In the present analysis, the principles for detecting vascular territory were based on the Voronoi decomposition method [13, 14]. In the liver, the Voronoi decomposition method has been tested in several evaluations and in more than 6,500 clinical cases since 2002 [14, 22, 23]. The U.S. Food and Drug Administration (FDA) approved these tools for preoperative planning for liver surgery. In the urological field, Isotani et al. reported that the tool was beneficial for predicting arterial territories with 100% sensitivity and 72.5% specificity by using Voronoi decomposition [15], and they stated that the predicted renal parenchymal volume correlated more significantly with the actual resected specimen volume ($r = 0.745$, $p < 0.001$) compared to our results ($r = 0.445$, $p < 0.001$). This difference in results might be due to differences in the sizes and/or positions of the renal tumors.

In the present study, Category I was significantly correlated with Category II with regard to renal parenchymal preservation. Conversely, Category III was significantly correlated only with renal functional preservation. These results indicate that there were some dysfunctional territories of postoperative renal volume. The discrepant results between categories indicate that it would be difficult to physically judge the functional residual renal volume after PN. On the other hand, our findings confirmed that the total residual renal function would not change markedly. When we predict the residual renal function at the affected kidney, renorrhaphy and resulting traumatic lesions would be more important than the resected tumor volume.

Several studies have considered the influence of compensatory hypertrophy on residual renal function after PN [12]. The same compensatory hypertrophy mechanism would occur to recover total residual re-

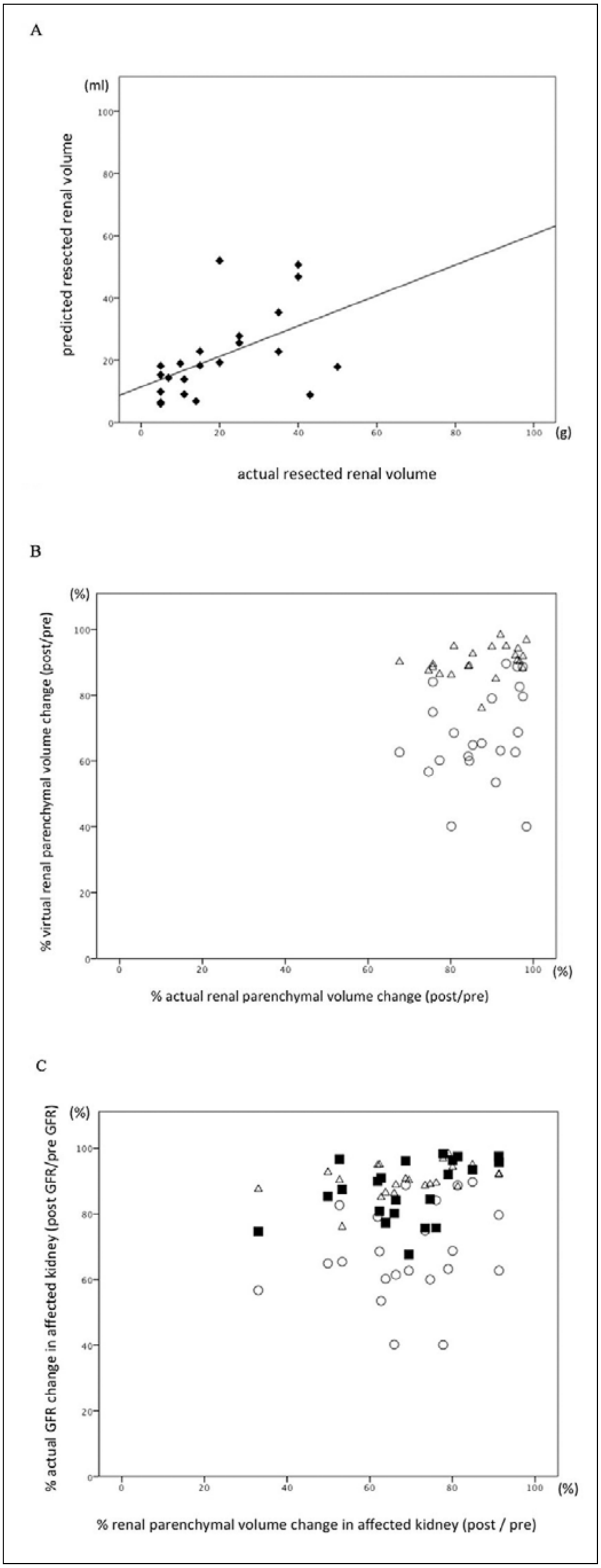

Figure 3. (A): *The predicted virtual resected volume including tumor was significantly correlated with the actual resected specimen volume ($r = 0.445$, $p < 0.001$).* **(B):** *Change in residual renal function of the affected kidney for renal mass was proportional to the amount of residual parenchyma removed. The change in virtual residual renal volume removed with the tumor and surgical margin (Category II) was significantly correlated with the actual change in residual renal volume ($r = 0.435$, $p < 0.05$).* **(C):** *The predicted residual renal volume change, excluding the surgical margin and irreversible ischemic territory (Category III), was significantly correlated with the actual residual renal function change ($r = 0.401$, $p < 0.05$). Solid line represents simple regression. Square, triangle, and circle represent Categories I, II, and III, respectively.*

nal function. It might not be easy to assess the residual renal function of each kidney in bilateral kidney cases, but our findings and the system we used to visualize the vascular territory might be more useful to predict the postoperative residual renal function in special cases such as a solitary kidney or kidney transplantation which are not influenced by contralateral hypertrophy. To our knowledge, many studies have emphasized minimizing the loss of nephron tissue, but there are no reports that focus on the renal vascular territory related to PN.

The present study is the first report to clarify the relationship between the parenchymal vascular territories and renal function. The techniques used in the present patient population prevented damage to the renal branch and vessels and kept the renal vascular flow as normal as possible. Alessandro et al. compared the surgical features of the use of a TachoSil® Fibrin Sealant Patch and those for FloSeal Hemostatic Matrix, in addition to surgical characteristics (open vs. minimally invasive, standard PN vs. enucleation, and suturing of the parenchymal defect) in patients who underwent PN without hemostatic agents [24]. They reported no detectable differences in medical or surgical complication rates, transfusion, or re-intervention after bleeding, or in the variations between pre- and postoperative hemoglobin levels and glomerular filtration rate, either overall or pairwise. We propose that to preserve renal function during PN, different tumor and hemostatic resection techniques should be considered and used, including minimal suturing of the edge of the renal arterial branch, soft coagulation, and the use of hemostatic agents without suture.

In the present study, the tumor volume and resected margin was relatively small. Further research regarding many types of tumor is necessary. This study is limited by its retrospective design and by its single-center design. In addition, it should be kept in mind that the effects of suture tension on the intervening parenchyma may result in additional tissue loss. The actual postoperative renal parenchyma preservation may decrease if the follow-up interval is set at >6 months. Although we found that the volumetric software was easy to use and we have confidence in our results, there may be some interobserver variability in measuring volumes. For example, hypovascular tumors were not clearly enhanced, and this 3D system did not indicate the tumor location and margins precisely. We were unable to determine the rate of recurrence and the differences in residual renal functional recovery within the postoperative period of 6 months. In addition, although a compensatory renal volume increase might affect the accuracy of postoperative residual renal function predictions, it was not considered in this study.

CONCLUSIONS

We determined the correlation between the renal functional preservation and the renal parenchymal preservation of the kidney of patients who had undergone partial nephrectomy surgery, and our analyses indicated that renorrhaphy and the resulting traumatized areas would be more important than the resected tumor volume. This 3D volumetric technique might allow an accurate preoperative prediction of the postoperative eGFR of the operated kidney. Further prospective studies are needed to obtain more definitive evidence, and a multicenter cooperative study is warranted to demonstrate the clinical utility of the technique.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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