Received:
07 June 2017

Revised:
22 October 2017

Accepted:
07 November 2017

<https://doi.org/10.1259/bjr.20170425>

Cite this article as:

Park BH, Cho KJ, Kim JI, Bae SR, Lee YS, Kang SH, et al. A useful method for assessing differences of compensatory hypertrophy in the contralateral kidney before and after radical nephrectomy in patients with renal cell carcinoma: ellipsoid formula on computed tomography. *Br J Radiol* 2018; **91**: 20170425.

FULL PAPER

A useful method for assessing differences of compensatory hypertrophy in the contralateral kidney before and after radical nephrectomy in patients with renal cell carcinoma: ellipsoid formula on computed tomography

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Objective: To investigate the usefulness of the ellipsoid formula for assessing compensatory hypertrophy of the contralateral kidney on pre-operative and post-operative CT in renal cell carcinoma (RCC) patients.

Methods: We retrospectively identified 389 patients who had radical nephrectomy for RCC between 2011 and 2015. Contrast-enhanced CT was performed within 3 months pre-operative and at 1 year post-operative. The kidney volumes were calculated from CT using the ellipsoid formula. We subdivided patients into three groups based on tumour size (I: ≤ 4 cm, II: 4–7 cm, III: > 7 cm). Volumetric renal parameters were compared and multivariate analyses were performed to determine predictors associated with pre-operative and post-operative compensatory hypertrophy.

Results: Kidney volume calculation using the ellipsoid method took a median of 51 s. Group III had a significantly larger median pre-operative contralateral renal

volume than Groups I and II (I: 140.4, II: 141.6, III: 166.7 ml, $p < 0.05$). However, the median ratio of post-operative contralateral renal volume change was significantly higher in Groups I and II than Group III (I: 0.36, II: 0.23, III: 0.12, $p < 0.001$). On multivariate analysis, tumour size revealed the strongest positive association with pre-operative contralateral kidney volume (partial regression coefficient: $\beta = 30.8$, > 7 cm) and ratio of post-operative contralateral kidney volume change ($\beta = 0.214$, I vs III; $\beta = 0.168$, II vs III).

Conclusion: Kidney volume calculation for assessing pre- and post-operative compensatory hypertrophy of the contralateral kidney in RCC patients can be easily and rapidly performed from CT images using the ellipsoid formula.

Advances in knowledge: The ellipsoid formula allows reliable method for assessing pre-operative and post-operative compensatory hypertrophy of the contralateral kidney in RCC.

INTRODUCTION

Historically, the standard surgical management of renal cell carcinoma (RCC) has been radical nephrectomy. Although the biological mechanism that underlie this phenomenon is not well understood, contralateral hypertrophy is an important aspect for estimating global renal function after nephrectomy.¹ Renal volume is regarded as the most precise indicator of kidney size² and also correlates with renal function.^{3,4}

CT, ultrasound sonography and MRI are commonly used to estimate the renal volume. However, ultrasound sonography is associated with substantial intra- and interobserver variation,^{5,6} and MRI is expensive, has limited accessibility, and is not always possible (e.g. pace maker, claustrophobia). The usefulness of CT to estimate renal volume has been highlighted by several studies.^{7,8} Previous studies that used CT for measurement of the kidney volume used the ellipsoid method or other methods requiring volume measuring software

or specialized post-processing.^{4,9–12} The latter methods can be time-consuming and not readily available despite of high accuracy.¹³ The former method is easy to perform; however, it raises the problem of systematic underestimation of kidney volumes.^{10,13,14}

A few previous studies have suggested modified method or correction factors to avoid underestimation of the renal volume by the ellipsoid formula.^{9,10,13} However, those studies were included relatively small number of patients and warranted prospective validation. In addition, patients included in those studies were potential donors or had kidneys without neoplastic abnormality.

Till now, the compensation hypertrophy on the contralateral normal kidney before and after nephrectomy through volumetric renal parameters estimated by the ellipsoid method in RCC patients has not been reported. Therefore, we investigated the usefulness of the ellipsoid formula for assessing compensation hypertrophy on the contralateral normal kidney before and after radical nephrectomy for RCC. Additionally, we analysed potential factors affecting compensation hypertrophy on the contralateral normal kidney before and after operation in RCC patients.

METHODS AND MATERIALS

Patients

This retrospective study was approved by the institutional review boards of the centres involved, and informed consent was obtained from all patients. A total of 389 patients underwent radical nephrectomy for RCC between March 2011 and May 2015 at two different university hospitals. Clinical data on age, sex, body mass index (BMI), American Society of Anesthesiologists score, diabetes mellitus (DM) and hypertension were collected at hospital admission for operation. Contrast-enhanced CT was performed within 3 months before surgery and 1 year post-operatively. The serum creatinine level was measured within 3 months of the operation and 1 year after radical nephrectomy. Tumour characteristics were defined as endophytic when less than 40% of the lesion extended off the surface of the kidney, mesophytic when between 40 and 60% of the lesion extended off the surface of the natural border of the kidney, and exophytic when more than 60% of the lesion extended off the natural outer surface of the kidney, based on pre-operative CT images.¹⁵ Glomerular filtration rate (GFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.¹⁶ We excluded patients with cystic renal masses or bilateral RCC and those without laboratory test results or pre-operative/post-operative contrast-enhanced CT, resulting in inclusion of a total of 324 patients in the study. Tumour T stage was classified according to the American Joint Committee on Cancer/Union for International Cancer Control tumour-node-metastasis system.¹⁷ The Fuhrman grading system was used to measure the nuclear grade.¹⁸ Tumour size was measured as the longest dimension of the tumour on CT images done before radical nephrectomy. We divided RCC patients into three groups to assess the impact of tumour size on the contralateral renal volume before or after radical nephrectomy (tumour size ≤ 4 cm, tumour size 4–7 cm, tumour size > 7 cm).

CT techniques and kidney volume calculation

CT examination was performed using a 128-detector CT scanner [Definition AS+; Siemens Medical Solutions, Forchheim, Germany ($n = 178$)] and 128-detector CT scanner [Discovery CT750 HD; GE Healthcare, Waukesha, MI ($n = 146$)]. All examination was performed in the craniocaudal direction including the region from the diaphragmatic dome to the pubic symphysis during suspended respiration with tube voltage of 100 or 120 kVp and tube current of 200 or 220 mA. All patients underwent three-phase (pre-enhanced, arterial and portal venous) CT imaging scans. A total of 120 ml of iodinated contrast agent (Ultravist 300; Bayer Healthcare, Berlin, Germany) was injected intravenously at a rate of $2\text{--}4\text{ ml s}^{-1}$. The portal venous phase was acquired 70 or 90 s after contrast administration. All transverse and coronal images were reconstructed with a section thickness of 3–5 mm.

The ellipsoid formula was used to calculate kidney volume (kidney volume = $\pi/6 \times \text{length} \times \text{width} \times \text{thickness}$). One radiologist and one urologist, who were blinded to patient clinical information, measured the length, width, and thickness of the kidney on the picture archiving and communication system workstation with dedicated software (M-view 5.4; Marotec Medical System, Seoul, Korea or ViewRex; TechHeim, Seoul, Korea). All kidney volumes were measured on the portal venous phase CT images. Kidney width and thickness were estimated on the largest axial image. Kidney width was measured from the lateral border of the kidney to the renal sinus and kidney thickness was measured vertical to this plane (Figure 1a). Kidney length was measured as the maximum longitudinal length on the coronal reconstruction images (Figure 1b). The measurement was performed two times for each kidney for the radiologist, and the kidney volume was based on the mean value of the two results.

Statistical analyses

Continuous data are expressed as median interquartile range (IQR), and categorical data are expressed as absolute values (percentages). The demographic and clinicopathologic variables among the three groups were compared using the χ^2 test and one-way ANOVA test. The one-way ANOVA test was used to compare the volumetric parameters among the tumour size groups. Changes in median contralateral kidney volume from before radical nephrectomy to 1 year after radical nephrectomy among the three groups were analysed.

Figure 1. Measurement of kidney volume via the ellipsoid method. (a) Mediolateral diameter (width) measured from the lateral border of the kidney to the renal sinus and perpendicular anteroposterior diameter (thickness) on the axial image. (b) The longest diameter (length) of the kidney measured on the coronal image.

Table 1. Characteristics of patients who underwent radical nephrectomies

	Total (%)	Tumour size			<i>p</i> ^a
		≤4 cm, No. (%)	4 cm < size ≤7 cm, No. (%)	>7 cm, No. (%)	
No. of patients	324 (100)	116 (35.8)	116 (35.8)	92 (28.4)	
Median age (IQR)	57 (49–65)	55 (49–64)	59 (49–67)	54 (48–66)	0.230
Sex					0.059
Male	204 (63.0)	70 (60.4)	66 (56.9)	68 (73.9)	
Female	120 (37.0)	46 (39.6)	50 (43.1)	24 (26.1)	
Median kg m ⁻² BMI (IQR)	24.2 (22.3–26.7)	24.9 (22.7–26.7)	24.3 (22.7–26.8)	23.4 (21.9–26.6)	0.066
ASA score					0.753
1	98 (30.2)	38 (32.8)	34 (29.3)	26 (28.3)	
2–3	226 (69.8)	78 (67.2)	82 (70.7)	66 (71.7)	
Diabetes mellitus	62 (19.1)	26 (22.4)	18 (15.5)	18 (19.6)	0.407
Hypertension	80 (24.7)	29 (25.0)	32 (27.6)	19 (20.7)	0.819
Median mg dl ⁻¹ pre-op creatinine (IQR)	0.90 (0.76–1.09)	0.85 (0.76–1.00)	0.93 (0.75–1.14)	0.93 (0.76–1.10)	0.048
Median ml min ⁻¹ 1.73 m ⁻² pre-op GFR (IQR)	81.1 (66.7–97.8)	83.2 (73.0–93.4)	79.1 (63.3–89.9)	78.9 (64.3–96.1)	0.033
Median mg dl ⁻¹ post-op creatinine (IQR)	1.25 (1.05–1.42)	1.30 (1.08–1.49)	1.21 (1.04–1.41)	1.21 (1.03–1.33)	0.012
Median ml min ⁻¹ 1.73 m ⁻² post-op GFR (IQR)	56.8 (50.5–66.5)	54.5 (46.1–61.6)	56.7 (51.6–67.0)	61.0 (54.7–71.0)	0.002
Tumour side					0.877
Right	150 (46.3)	54 (46.6)	52 (44.8)	44 (47.8)	
Left	174 (53.7)	62 (53.4)	64 (55.2)	48 (52.2)	
Tumour characteristics					<0.001
Exophytic	110 (34.0)	18 (15.5)	40 (34.4)	52 (56.5)	
Mesophytic	80 (24.7)	24 (20.7)	38 (32.8)	18 (19.6)	
Endophytic	134 (41.3)	74 (63.8)	38 (32.8)	22 (23.9)	
Median cm tumour size (IQR)	4.8 (3.5–7.4)	3.0 (2.2–3.5)	5.0 (4.5–6.0)	9.0 (7.7–10.1)	<0.001
Fuhrman grade					<0.001
1–2	92 (28.4)	49 (42.2)	28 (24.1)	15 (16.3)	
3–4	232 (71.6)	67 (57.8)	88 (75.9)	77 (83.7)	
Histology					0.032
Clear cell	285 (88.3)	104 (89.7)	107 (87.9)	74 (80.5)	
Papillary	16 (4.9)	5 (4.3)	4 (3.4)	7 (7.6)	
Chromophobe	14 (4.0)	4 (3.4)	4 (3.4)	6 (6.5)	
Other	9 (2.8)	3 (2.6)	1 (0.9)	5 (5.4)	

BMI, body mass index; GFR, glomerular filtration rate.

^aOne-way analysis of variance test for continuous variables and Pearson χ^2 test for categorical variables.

Univariate and multivariate linear regression analyses were performed to determine predictive factors in association with compensatory hypertrophy of the contralateral kidney before and after surgery in patients. Inter- and intraexaminer reliability was assessed by intraclass correlation coefficient analysis. The coefficients were calculated with 95% confidence intervals (CIs). $p < 0.05$ indicated statistical significance.

Statistical analyses were performed using SPSS, v. 13.0 (SPSS Inc, Chicago, IL).

RESULTS

The clinicopathologic characteristics of the 324 patients who had a radical nephrectomy are showed in Table 1. The median age of patients was 57 years (IQR 49–65). The median pre-operative

Table 2. Pre- and post-operative volumetric parameters in patients with renal cell carcinoma according to tumour size

Parameters	Median (IQR)			<i>p</i> -value ^a		
	I: ≤4 cm	II: 4 cm < tumour size ≤7 cm	III: >7 cm	I vs II	I vs III	II vs III
Pre-operation						
Contralateral kidney volume, ml	140.4 (116.8–160.2)	141.6 (123.1–165.6)	166.7 (133.9–193.2)	0.651	0.023	0.032
1 year after operation						
Contralateral kidney volume, ml	181.5 (156.1–202.9)	181.1 (161.8–204.1)	187.5 (162.6–216.9)	0.975	0.625	0.436
Contralateral kidney volume, ml (post-operative – pre-operative)	36.8 (23.4–65.3)	35.2 (24.4–53.7)	20.8 (8.9–41.6)	0.723	0.075	0.116
Contralateral kidney volume change ^b	0.36 (0.18–0.45)	0.23 (0.15–0.38)	0.12 (0.02–0.19)	0.236	<0.001	<0.001

^aOne-way analysis of variance test for continuous variables.

^bContralateral kidney volume change = (post-operative contralateral kidney volume – pre-operative contralateral kidney volume)/pre-operative contralateral kidney volume.

creatinine level was 0.90 mg dl⁻¹ (IQR 0.76–1.09), and the median pre-operative CKD-EPI GFR was 81.1 ml per min per 1.73 m² (IQR 66.7–97.8). The median tumour size was 4.8 cm (IQR 3.5–7.4). The most common histology was clear cell in 285 patients (88.3%), followed by papillary in 16 patients (4.9%) and chromophobe in 14 patients (4.0%). Age, American Society of Anaesthesiologists score, gender, BMI and presence of DM or hypertension were not statistically different between the groups. Patients with RCC larger than 7 cm were more likely to have lower pre-operative CKD-EPI GFR, higher Fuhrman grade and non-clear cell histologic type.

The kidney volume calculation using the ellipsoid formula took a median of 51 s. The median pre-operative contralateral normal kidney volume was greater in Group III than in Group I and II (III vs I, 166.7 vs 140.4 ml, *p* = 0.023; III vs II, 166.7 vs 141.6 ml, *p* = 0.032). However, there were not significant differences in the median contralateral kidney volume 1 year after nephrectomy or the median post-operative contralateral kidney volume change between the groups (*p* > 0.05). Unlike other post-operative volumetric parameters, the median ratio of post-operative contralateral normal kidney volume change was significantly higher in Group I and II than in Group III (I vs

III, 0.36 vs 0.12, *p* < 0.001; II vs III, 0.23 vs 0.12, *p* < 0.001, Table 2). Contralateral renal volume 1 year after nephrectomy was correlated with post-operative CKD-EPI GFR (*r* = 0.348, *p* = 0.001) in Figure 2. Interclass correlation coefficient for interobserver reliability was 0.958 [95% CI (0.934 to 0.969)] and intraobserver interclass correlation coefficient was more excellent, 0.97 [95% CI (0.962 to 0.974)].

Univariate and multivariate linear regression analyses of potential factors affecting pre- or post-operative compensation hypertrophy on the contralateral kidney of RCC patients are listed in Table 3. Multivariate regression analyses showed that increased contralateral renal volume before nephrectomy was positively correlated with higher BMI (*p* < 0.001), DM (*p* = 0.002) and tumour size (>7 cm) (*p* = 0.001), and was negatively correlated with older age (*p* = 0.036). Tumour size larger than 7 cm (partial regression coefficient: β = 30.8) was the most important predictor associated with an increase of the pre-operative contralateral renal volume. In addition, multivariate regression analyses showed that a higher median ratio of volume change of the contralateral normal kidney at 1 year after surgery was positively associated with male gender (*p* = 0.007) and tumour size (≤4 or 4–7 cm) (*p* < 0.001). Tumour size (≤4 cm or 4–7 cm) showed the strongest association with the increased ratio of postoperative contralateral renal volume change (I vs III, β = 0.214; II vs III, β = 0.168, respectively, *p* < 0.001).

DISCUSSION

In this study, we found that tumour size was the strongest independent predictor of compensation hypertrophy on the contralateral kidney through estimated kidney volume analysis using an ellipsoid formula with multi-detector CT measurements before and after surgery in RCC patients.

We identified that the median pre-operative contralateral normal kidney volume of patients with tumour size >7 cm was significantly greater than that of patients with tumour size 4–7 or ≤4 cm. We also identified that the median post-operative contralateral renal volumes between the groups were not significantly different. However, the median ratio of the contralateral renal volume changes in patients with tumour size 4–7 cm and ≤4 cm were significantly greater than patients

Figure 2. Relationship between post-operative GFR and post-operative contralateral kidney volume. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate.

Table 3. Linear regression analyses of factors with an impact on pre-operative or post-operative compensatory hypertrophy of the contralateral kidney in renal cell carcinoma patients

Parameters	Univariate		Multivariate	
	β	<i>p</i> -value	β	<i>p</i> -value
Before nephrectomy ^a				
Age (continuous)	−0.541	0.107	−0.809	0.036
Gender (M vs F)	11.386	0.164	5.003	0.629
Body mass index (continuous)	4.587	<0.001	4.748	<0.001
Diabetes mellitus (vs no)	31.493	0.002	30.707	0.002
Hypertension (vs no)	5.978	0.450	0.201	0.981
GFR (continuous)	0.192	0.331	0.170	0.513
Tumour size (vs ≤4 cm)				
4 cm < size ≤7 cm	3.062	0.305	3.004	0.739
>7 cm	21.558	<0.001	30.813	0.001
After nephrectomy ^b				
Age (continuous)	−0.004	0.001	−0.002	0.107
Gender (M vs F)	0.095	0.006	0.089	0.007
Body mass index (continuous)	0.004	0.351	0.004	0.362
Diabetes mellitus (vs no)	−0.012	0.684	−0.037	0.287
Hypertension (vs no)	−0.040	0.145	−0.016	0.568
GFR (continuous)	0.002	0.014	0.001	0.174
Tumour size (vs >7 cm)				
≤4 cm	0.127	<0.001	0.214	<0.001
4 cm < size ≤7 cm	0.044	0.026	0.168	<0.001

GFR, glomerular filtration rate.

^aDependent variable: contralateral normal kidney volume.^bDependent variable: contralateral kidney volume change.

with tumours >7 cm at 1 year after nephrectomy (I vs III, 0.36 vs 0.12; II vs III, 0.23 vs 0.12, respectively, $p < 0.001$). These findings are consistent with results of previous studies using CT and volumetry software, which demonstrated pre-operative compensation hypertrophy of the contralateral normal kidney is more noticeable in patients with tumour size >7 cm and compensation hypertrophy on the contralateral normal kidney at 1 year after nephrectomy is more apparent in patients with tumour size 4–7 cm and ≤4 cm.^{11,12} This indicates that, in patients with tumour size >7 cm, the contralateral kidney initiates compensatory hypertrophy before surgery in response to a great normal parenchyma loss on the diseased kidney¹⁹ and in patients with tumour size 4–7 cm or ≤4 cm, the contralateral kidney does not start to compensate before surgery because of decreased normal parenchyma loss on the tumour side, but rather starts after surgery in response to sensing the normal parenchyma loss on the tumour side.¹²

Several studies have suggested potential factors that contribute to compensation hypertrophy of the contralateral kidney before nephrectomy, including BMI, gender, pre-operative GFR, DM, age and tumour size (>7 cm),^{3,11} after surgery, such as (body surface area)BSA, age, comorbidity, pre-operative contralateral

kidney volume, post-operative GFR, gender and tumour size (≤4 or 4–7 cm).^{3,4,12,20,21} The predictive factors identified using an ellipsoid formula with CT measurements in our study were in agreement with those suggested from previous studies using CT and volumetry software.

To the best of our knowledge, this is the first study in which kidney volume calculation from the ellipsoid equation on pre- and post-operative CT images were used to show that compensation hypertrophy of the contralateral normal kidney in RCC patients begins after or before radical nephrectomy depending on tumour size.

Ultrasound sonography, MRI and CT have been used to estimate renal volume, and all these methods are associated with prediction errors, the least being with CT.^{2,22} Several reports have shown that renal volumes calculated by the ellipsoid formula on CT images underestimate the renal volumes by approximately 8.2–22.2% compared with those measured using volumetry softwares.^{10,13,14} Renal volume estimated by the ellipsoid equation does not take into consideration the complex anatomy and shape of the kidneys and seems to systematically underestimate kidney volume.^{6,23} Therefore, CT estimates of length, width and

thickness could lead to a prediction error for kidney volume using the ellipsoid method because the combination of these values is affected similarly.⁵

Despite the underestimation of the ellipsoid method for absolute kidney volume calculation, our data for compensatory hypertrophy by volume calculation of the contralateral kidney without ellipsoid formula modification or correction factor are in good agreement with the results based on CT and volumetry software. Several methodological differences could explain the good agreement. First, the renal length of CT in our study was measured not from transverse slices by multiplying the image thickness by the number of images between lower and upper poles of the kidney but from the coronal section. It was demonstrated that the accuracy of lengthwise measurements was better with coronal CT sections than with transverse CT sections.²² Second, the ellipsoid formula was used to calculate the difference and ratio of the contralateral kidney volumes. Therefore, the methodical underestimation of individual pre-operative and post-operative volumetric parameters from the ellipsoid equation should not negatively affect the results.

The ellipsoid equation remains appealing because it is easy to use and does not require the use of post-processing software.¹⁰ The ellipsoid method was also shown to be faster than other methods of kidney volume estimation requiring special software.¹³ In general, kidney volume measurements have been considered time-consuming, particularly when kidney contours require direct planimetry.⁹ Several studies have reported a total post-processing time of 5 to 16 min despite the use of semiautomated segmentation software.^{24–26} However, other reports have suggested that the ellipsoid method takes an average of approximately

53–60 s and was not subject to manual corrections.^{9,24} The time for kidney volume calculation in our study (median 51 s) was consistent with that reported previously.

The present study had a few limitations. First, our study was retrospective in design and compared with the previous literature results using volumetry software. Second, we used two different CT vendors from two institutions (Uijeongbu St. Mary's hospital and Bucheon St. Mary's hospital) to acquire images. However, the differences in estimation of renal volumes between the two CT machines would have minimal effect because the two institutions used similar quality CT scanners and a similar CT protocol. Finally, we used the CKD-EPI equation to calculate GFR. There are different methods available to calculate GFR. Therefore, GFR calculated using different methods may cause discrepancies. Additional evidences are required to confirm our findings

CONCLUSIONS

We identified that the ellipsoid formula provided a clinically appealing method of kidney volume calculation on CT images with short image post-processing time and had good agreement with previously reported results using volumetry software. In addition, renal parenchymal volume estimated by an ellipsoid formula with CT measurements correlated well with post-operative kidney function, and it could be useful to evaluate the compensation hypertrophy on contralateral normal kidney after surgery in RCC patients. Also, our data confirmed that tumour size was the most significant factor associated with compensation hypertrophy of the contralateral normal kidney before and after radical nephrectomy for RCC. Knowledge for usefulness of the ellipsoid formula would be valuable in future clinical studies included kidney volume calculation.

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