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Validation of 3-D Volumetric Based Renal Function Prediction Calculator for Nephron Sparing Surgery

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Abstract

Objective—To evaluate a recently published volume-based renal function prediction calculator intended to be used in small renal mass surgical counseling.

Methods—Retrospective data collection included 3-dimensional calculation of renal mass and parenchyma of patients who have undergone extirpative therapy. The predicted glomerular filtration rate (GFR) was calculated using the online calculator. The predicted GFR was compared with the actual 6-month GFR. The Pearson correlation coefficient, paired T-test and root mean square error (RMSE) are utilized for statistical analysis.

Results—After institutional review board approval, 3 institutions provided data for analysis. After patients with renal mass size >300 cc, renal size >400 cc, or preoperative CKD stage 3 had been excluded, we retrospectively analyzed data from 136 patients. The median mass volume was 22.2 cc (IQR 7-49). In multiple linear regression analysis, the most significant variables predicting postoperative GFR were partial vs. radical nephrectomy and preoperative GFR with an overall R² of 0.68 (F = 26.13, P < .001). The predicted GFR was 75.4 mL/min/1.73 m² compared to an actual GFR of 70.7 mL/min/1.73 m² (P < .001, paired T test). The predicted GFR was highly correlated

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Compliance with Ethical Standards: None of the authors have potential conflicts of interest with the material in this manuscript. Our research did not involve Human Participants and/or Animals. Our research was conducted retrospectively from charts and images and did not change any medical care of the patients. Due to the retrospective nature, each institution did complete a non-human participant IRB and did not require Informed consent.

with the actual post-operative GFR at 6 months (Pearson correlation, $r=0.65$, $P < .001$). RMSE of the validation cohort was 16.87.

Conclusions—The Predictive Tool to Determine Renal Function Benefit of Nephron Sparing Surgery Compared to Radical Nephrectomy online calculator effectively predicts GFR and could potentially be used to help urologists and patients discuss renal function prior to extirpative renal surgery.

Keywords

Renal Mass; Renal Cancer; Chronic Kidney Disease; Calculator; Partial Nephrectomy

Introduction

An estimated 64,000 new renal cancer diagnoses and nearly 50,000 renal surgeries are performed each year in the United States.[1,2] However, nephron-sparing surgery (NSS) is underutilized, considering only 20% of all extirpative renal surgeries performed in the United States are partial nephrectomies.[3] Despite improved imaging leading to stage migration more feasible to NSS and guideline recommendations encouraging NSS, the adoption of such surgery has been slow.[4-9,2]

NSS has the potential to spare kidney tissue and prevent significant chronic kidney disease (CKD) thereby potentially impacting future overall health.[10] CKD plays an important role in overall morbidity and mortality in many groups of patients.[11] Additionally, NSS results in equivalent outcomes to radical nephrectomy in patients with cancer.[12,13] However, various patient and surgeon specific factors may influence clinical decision-making regarding the actual use of NSS. [14-16]

Previous studies have shown that a preoperative kidney volume derived from computer-assisted techniques has prognostic significance for post-operative eGFR.[17,18] We propose that using preoperative factors to predict a future renal function may be useful in shared decision-making with regards to NSS. Herein, we investigate the ability of an online point-of-care calculator using preoperative demographics and volumetrics in a “real world” validation to predict postoperative renal function.

Methods

Population

After institutional review board approval, we formed a multi-site collaborative group to enroll urologic oncology patients diagnosed with clinical tumor stage 1 cortical renal neoplasms suspicious for renal cell carcinoma (RCC) and who underwent surgical excision (RN or NSS) from 7/8/2009 to 9/4/2014. The patients were retrospectively selected using specific selection criteria from three institutions: Memorial Sloan Kettering Cancer Center (MSKCC), University of California Irvine (UCI) and the University of Texas Health Science Center San Antonio (UTHSCSA). Patients were excluded if they had CKD stage 3 or greater. To ensure accurate assessments, CT scans had to be formatted to the institutions' 3-D formatting system, with 2.5-mm cuts if possible. The CT scans also needed to have

contrast due to some systems utilizing a Hounsfield unit detection of similar tissues. Patients had to have approximately 6 months of renal functional outcomes and clinical follow up data. Demographic data, including renal function and radiographic data were collected.[19] Renal function was evaluated by creatinine and the estimated glomerular filtration rate (eGFR) as calculated by the Modification of Diet in Renal Disease (MDRD) equation.[20]

Volumetric Assessment

CT was performed on both 16- and 64-detector multi-detector CT scanners at the 3 institutions. Images were reconstructed to 2.5-mm to 5-mm thin sections when available, or otherwise as close to these values as possible. The preoperative CT scans were uploaded into commercially available 3D volume rendering and calculation programs, which included TeraRecon Software (Foster City, CA; MSKCC) Vitrea Software (Minnetonka, MN; UCI), and Volume Tracing in Advanced Vessel Analysis, Philips Healthcare (Alpharetta, GA; UTHSCSA). An example of the 3-D volume rendering software from Phillips is noted in Figure 1. The tumor volume is first obtained followed by the volumetric rendering of the affected kidney excluding the area of the tumor. Lastly, the contralateral kidney is then assessed for total volume. The volumetric software was directly observed to correct for overlapping renal pelvis and vasculature structures that should be excluded from the parenchymal assessment. Exclusion of patients with renal mass size >300 cc, renal size >400 cc, or preoperative CKD stage 3 or greater was established using in the initial validation of the calculator due to poor predictive value at the extremes of volumes.[21]

Online GFR Calculator

Predicted GFR values were calculated using the online calculator: “Predictive Tool to Determine Renal Function Benefit of Nephron Sparing Surgery Compared to Radical Nephrectomy” available at <https://kidneycancersurgery.shinyapps.io/webapp/> (Figure 2). External validation of this tool has previously been published.[21] The current study confirms these findings in utilizing currently available 3-D rendering software systems.

Statistical Analysis

The predicted GFR was compared with the actual 6-month GFR. A 6-month time period was utilized in order to allow the renal system to stabilize would likely be too soon for compensatory hypertrophy to affect our eGFR outcomes. A recent publication on the natural history of kidney function on over 1,300 patients in a Canadian cohort noted that the renal function stabilized at 3 months and remained the same over a 24-month period.[22] The root mean square error (RMSE) was the primary validation test. The Pearson correlation coefficient was used as an indication of GFR correlation from predicted to actual 6-month GFR. The paired T-test was used to determine how close the GFR prediction was to the actual 6-month value. Linear regression analysis was used to identify the overall fitness of the equation and to identify the most significant factors contributing to postoperative GFR other than preoperative GFR.

Results

Population and Analysis

After institutional review board approval, three institutions provided data for analysis. We retrospectively analyzed data from 136 patients. Only 17 (12.5%) patients had a radical nephrectomy. Demographics are displayed in Table 1. The median mass volume was 22.2 cc (IQR 7-49). In our study, a volume ranging from 20-30 cc³ was equivalent to a diameter average of 3.8 cm × 3.6 cm × 3.6 cm. In multiple linear regression analysis, the most significant variables predicting postoperative GFR were partial vs. radical nephrectomy and preoperative GFR with an overall R² of 0.68 (F = 26.13, *P* < .001). Independent of the preoperative GFR, the residual volume of the affected kidney (*P* < .001) and the volume of the mass (*P* < .001) were statistically significant contributors of 6-month postoperative creatinine.

Clinical Decision Tool and Performance

The predicted GFR was 75.4 mL/min/1.73 m² compared to an actual GFR of 70.7 mL/min/1.73 m² (difference of 4.7 mL/min/1.73 m², *P* < .001, paired T test). The predicted GFR was highly correlated with the actual post-operative GFR at 6 months (Pearson correlation, *r*=0.65, *P* < .001, Figure 3). These results held true when separating the groups who had partial nephrectomy (*r*=0.64, *P* < .001) and a little better for those with radical nephrectomy (*r*=0.76, *P* < .001). While the correlation was better with radical nephrectomy the RMSE was 20.4, largely due to the difference in predicted to actual GFR median of -16.4 (SD 12.8). RMSE was improved for partial nephrectomies 16.36 with a median GFR difference of -8.3 (SD 16.1). The overall (radical and partial nephrectomies combined) RMSE of the validation cohort was 16.87, which is similar to the original RMSE of the calculator of 15.

Discussion

We have validated a point-of-care clinical tool to assist clinicians in predicting postoperative estimated GFR through the use of a database obtained from retrospective analysis of 3 institutions with 3 different acquisition software programs. The equation was reliable and adequately predicted GFR and subsequent CKD after surgery. However, the calculator did overestimate the eGFR. While calculator performed better when partial nephrectomy was the ensuing surgery it did correlate well with nephrectomy data as well. We will implement this data into the calculator and retest with a larger training cohort to provide more accurate data. Moreover, encouraging automated systems to provide volumetric data on renal tumors and parenchyma will allow more robust data collection and analysis in the future.

Because the data is available from the first CT scan obtained for diagnosis of a small renal mass, a volumetric assessment could be performed at that time. The urologist counseling the patient regarding radical vs. partial nephrectomy may now have additional, personalized data to provide recommendations regarding the risk of postoperative renal impairment. Personalized tools to assess risk of CKD are urgently needed. Traditionally, patients do not fully understand the association between nephron loss and the development of CKD and

proper counseling regarding NSS for the management of their early-stage kidney cancer needs improvement.[23]

Additionally, a meta-analysis has shown a possible survival benefit for partial nephrectomy in localized renal tumors.[24] Therefore, this online calculator may help discussing long-term ramifications of sparing renal function. While ischemia time is important and may need to be discussed in certain situations, the most important factor in predicting post-operative eGFR is parenchymal volume preservation.[25,26] The calculator focuses on what can be predicted preoperatively as a tool to assist in the discussion of postoperative renal function. Because ischemia is an intraoperative determinant, it would not play a role in this context. Moreover, in the development of the calculator ischemia time did not play a major factor in multivariable analysis.[21]

The only multicenter randomized clinical trial (EORTC 30904) comparing partial and radical nephrectomy oncologic outcomes did show a significant reduction in CKD with NSS.[27] However, a significant improvement in all-cause mortality was not, as anticipated, observed in a previous study showing increased mortality rates for each stage of CKD due to medical disease (CKD-M).[11] The concept of CKD-M and CKD from a surgical cause (CKD-S) has been described in a recent study by Lane and colleagues, and indicates that patients presenting with CKD-M who undergo renal surgery are at much higher risk for renal decline than those with CKD-S.[28] The long-term sequelae of patients who do not have CKD prior to renal extirpative surgery and later form CKD-M is unknown. However, the shared-decision making and discussion of anticipated CKD after surgery with potential anticipatory nephrology specialist involvement should be emphasized. We strongly recommend the use of these tools in the context of a prospective clinical trial.[29]

Limitations of our study include the inherent bias of a retrospective analysis and that physicians' preference and tumor size will influence outcomes. A margin added to the tumor volume may likely improve the prediction but this substantially adds to the processing time and development of computer programs to automate this process for future evaluation. We utilized different volumetric software at each institution intentionally in order to determine the applicability of the calculator across available in a real world application. However, this may contribute to variability and accuracy at different institutions. We also understand the variability in computed tomography between institutions could play a role in accuracy of the calculator; however, despite the variability the calculator maintained a robust predictive model. While we did perform a validation study, the previous data set only included partial nephrectomies. We attempted to include radical nephrectomies in this cohort but again only achieved a small number likely due to the high volume academic centers preference and referral pattern for partial nephrectomy contributing to the data. Additionally, we did not perform post-operative volumetric assessments to test the accuracy of the volumetric and surgical predictions of renal parenchymal preservation, which was performed in the development of the calculator.

Conclusion

The Predictive Tool to Determine Renal Function Benefit of Nephron Sparing Surgery Compared to Radical Nephrectomy online calculator is able to predict 6-month postoperative eGFR in the setting of partial or radical nephrectomy. The prediction of outcomes with the two approaches may be used in clinical decision involving and individualized assessment of predicted postoperative renal function. Future studies will include a prospective analysis to determine usefulness at the point-of-care.

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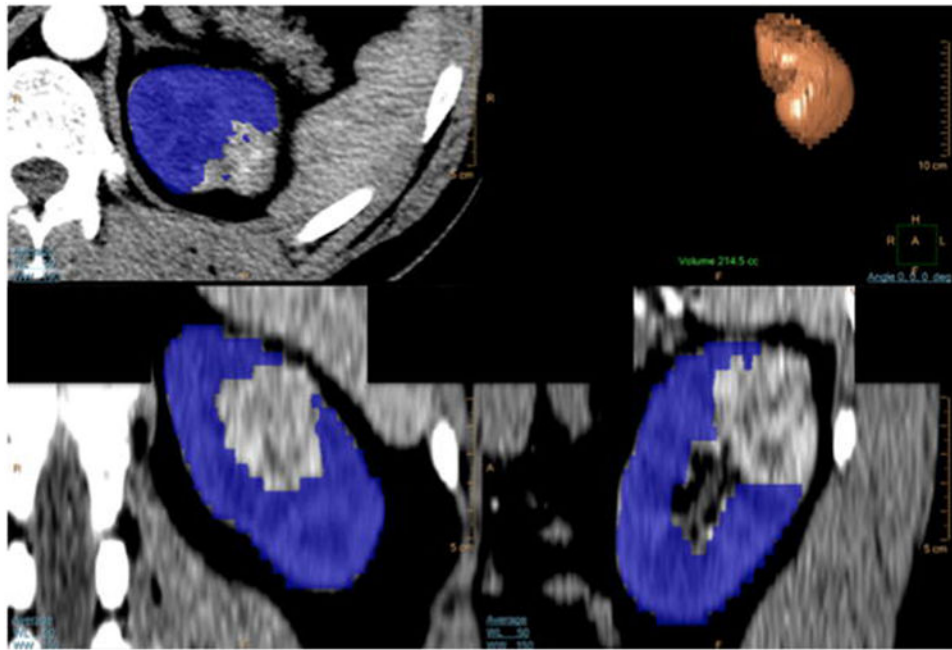


Figure 1. Renal volumetric assessment utilizing the volume tracing in advanced vessel analysis (Philips Healthcare)

The figure shows the left kidney with renal mass and surrounding parenchyma; i.e., ipsilateral spared parenchyma (blue). Additionally the volumes of the renal mass and contralateral kidney are obtained for use in the online calculator.

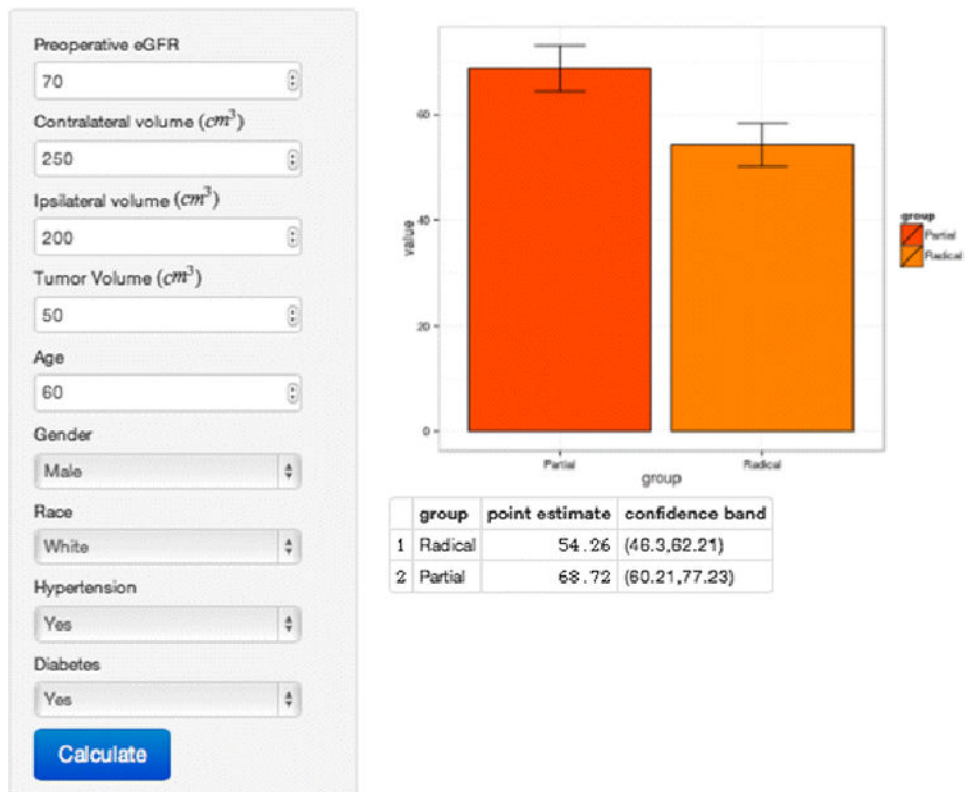


Figure 2. Predictive tool to determine renal function benefit of NSS compared to RN online calculator

The figure shows how the online calculator can be used in an office based setting. Once the radiologist provides the volumetric assessment of the kidney tumor, ipsilateral, and contralateral volumes, clinicians can put the numbers into the calculator along with GFR, age, gender, race/ethnicity, and extent of hypertension and diabetes. On the right side of the figure are two bar graphs. The red bar on the left is the predicted GFR if a partial nephrectomy were to be performed and the orange bar on the right indicates the predicted GFR if a radical nephrectomy were to be performed. The number values are indicated below the bar graph.

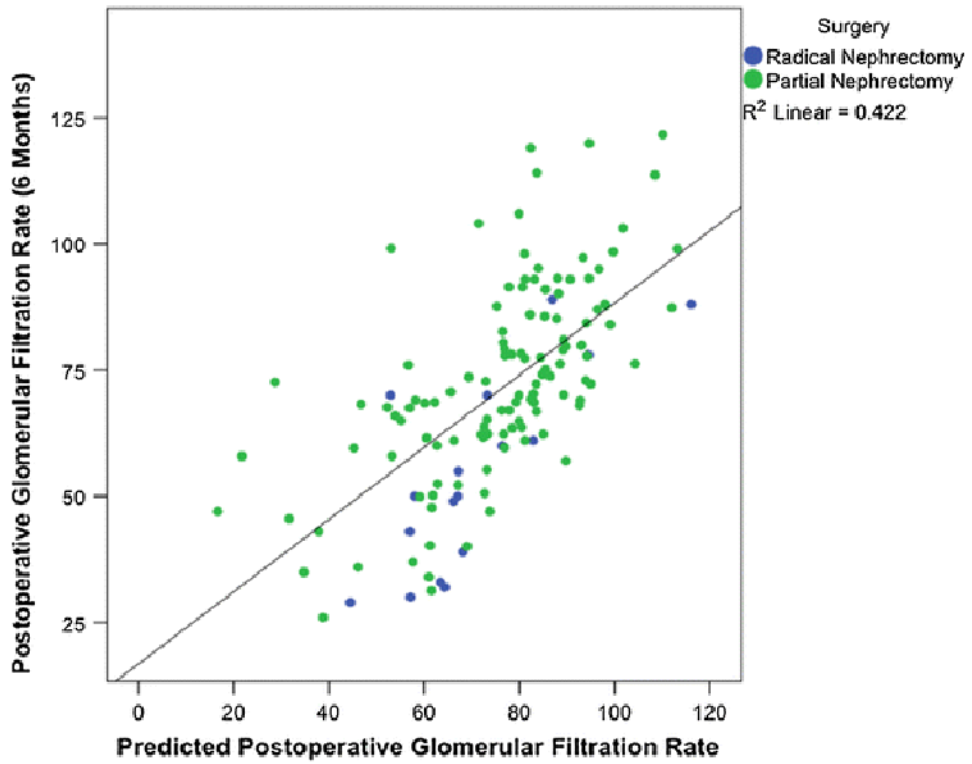


Figure 3. Scatter plot of calculator predicted vs. actual 6-month glomerular filtration rate
The figure represents predicted versus actual GFR for individual patients and which surgery they underwent (blue = radical and green = partial nephrectomy).

Table 1**Demographics**

Demographic (N=136)	Median (IQR) or N (%)
Age	57 (50 - 67)
Gender (male)	66 (46)
Ethnicity	
White	114 (83.8)
Black	8 (5.9)
Other	14 (10.3)
Hypertension	77 (56.6)
Diabetes	18 (13.2)
Volume of contralateral kidney (cc)	178.0 (147.6-200.7)
Residual volume of affected kidney (cc)	187.0 (155.8 - 229.5)
Volume of tumor (cc)	22.2 (6.8 - 49.4)
Preoperative creatinine	0.9 (0.8 - 1.0)
Postoperative creatinine (6 months)	1.0 (0.9 - 1.2)
Preoperative GFR	80.5 (69.0 - 94.6)
Postoperative GFR	70.0 (59.7 - 84.9)