Surgical Options for Localized Renal Cell Carcinoma, A Retrospective Clinical Study Based on Tumor Size

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Research

Keywords: Renal cell carcinoma, Radical nephrectomy, Nephron sparing surgery, Tumor size

Posted Date: July 12th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-689103/v1>

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Abstract

Purpose

Although many studies have explored the options of radical nephrectomy (RN) and nephron sparing surgery (NSS) for localized renal cell carcinoma (RCC), the answer to this question remains unclear. This study aims to compare the long-term prognostic differences between RN and NSS among different sizes of localized RCC.

Methods

This study retrospectively included 80,439 T1-T4 N0 M0 patients who underwent RN or NSS based on the Surveillance, Epidemiology, and End Results database. We calculated the 10-year overall survival (OS) and cancer specific survival of patients with RCC. We also evaluated the risk of cardiovascular death in patients using competing risk models for RN and NSS.

Results

Our analysis showed that patients who underwent NSS had a more prolonged OS of 5 and 10 years when the tumor size was less than 8.5cm and 7.2cm. Compared to RN, NSS does not appear to improve OS in large (> 7.2cm) RCC patients. And stratified analysis showed that NSS for RCC less than 9.2cm may be more likely to benefit from long-term OS in younger patients (<60 years), while RCC above 7.3cm may be more suitable for RN in older patients (>=60 years). The gender-stratified results suggested male and female patients may be more suitable for NSS for RCC below 6.4 and 7.7cm, respectively. Besides, competing risk models showed patients receiving RN have higher cumulative cardiovascular mortality.

Conclusions

For large RCC, NSS may be very carefully selected unless there are clear indications such as isolated congenital kidney and bilateral kidney cancer.

Introduction

Renal cell carcinoma (RCC) is one of the most common malignant tumors of the urinary system. As health screenings become more widespread, rising numbers of patients with RCC are found by abdominal imaging. Until now, surgery is still the first choice for patients with localized RCC without definite metastases. There are two main types of surgical approaches for RCC: radical nephrectomy (RN) and nephron sparing surgery (NSS). Due to new technologies such as segmental renal artery clamping(1,2) and the da Vinci robot and better preservation of renal function, NSS has been increasingly used in RCC treatment. To date, NSS has become standard therapy for patients with T1a RCC(3). However, it is still unclear which operation is preferred for T1b and T2 N0M0 kidney cancer(4).

Many studies have reported that NSS is more protective of renal function and reduces adverse cardiovascular events in patients relative to RN(5-7). And no differences were found between NSS and RN for tumor control(8-10). On the other hand, studies have shown that patients who received NSS were more likely to have a recurrent tumor(11), and more postoperative complications(12). However, most of these were retrospective studies with limited samples, and the only prospective randomized controlled trial study included only patients with RCC whose tumor size was less than 5 cm. Also, the current research only subclassified patients according to the stage, age, and so on. The choice of surgery for patients with different tumor sizes is still not reported. In kidney cancer, an increase in tumor size is related with an increased risk of malignancy(13-15). The selection of tumor size-based adjunctive surgical options may provide a new way of thinking for urologists.

In this study, we retrospectively analyzed the three-, five-, and ten-year overall survival (OS) of patients with different RCC sizes who underwent RN or NSS, based on the Surveillance, Epidemiology, and End Results (SEER) database. Furthermore, this study's findings may provide some guidance and assistance to urologists in selecting surgical approaches.

Materials And Methods

Patients selection

We employed the SEER*stat version 8.3.8 to screen RCC patients who received RN or NSS from 18 SEER registries across the United States. The ICD-O-3 site code: C64.9, kidney, renal pelvis, and ureter surgery code: NSS (Code 30) or RN (Code 40 and 50) were used to search for eligible patients for inclusion. Patients were excluded if they meet the following exclusion criteria: 1. unknown survival time, survival status and cause of death. 2. unknown TNM stage information and tumor size. 3. bilateral RCC, multiple primary carcinomas and RCC that has developed lymphatic or distant metastases. Finally, we enrolled 51,027 patients who received RN and 29,412 patients received NSS from 2004 to 2017. And the information of demographic characteristics and tumor statistics were also recorded, including age at diagnosis, race, Fuhrman grade and gender. OS was calculated from the date of diagnosis until death from any cause or until 2017. Patients diagnosed before 2010 were staged using the 6th edition of the TNM staging system, and patients diagnosed after 2010 were staged using the 7th edition of the TNM staging system.

Statistical analysis

Categorical variables are described using frequencies and ratios, and the Chi-square test was used to test for differences between the categorical variables. Fisher's Exact Test was used when the data do not meet the conditions for using the chi-square test. The R software "survival" package was used to calculate 5 and 10-year OS for patients with different tumor sizes who received RN and NSS, respectively. Scatter plots of survival for different tumor sizes were fitted to curves using the logistic regression. Cumulative incidence function was used to assess tumor- and cardiovascular-specific mortality in

patients undergoing RN or NSS. And Gray's test was used to examine whether there was a difference in cumulative mortality between patients undergoing RN and NSS. A two-sided P value of less than 0.05 was considered statistically significant.

Table 1. Patient characteristics.			
Variables	RN n (%)	NSS n (%)	P-value
Cases evaluated	51,027 (100)	29,412 (100)	
Age at diagnosis			<0.0001
< 50	1,0052 (19.7%)	7,827 (26.6%)	
50-59	1,3832 (27.1%)	8,380 (28.5%)	
60-69	1,4667 (28.7%)	8,481 (28.8%)	
70-79	9,307 (18.2%)	3,965 (13.5%)	
>=80	3,169 (6.2%)	759 (2.6%)	
Sex			0.156
Male	31,552 (61.8%)	18,038 (61.3%)	
Female	19,475 (38.2%)	11,374 (38.7%)	
Race			0.007
White	41,729 (81.8%)	23,879 (81.2%)	
Black	5,592 (10.9%)	3,220 (10.9%)	
Other and unknown	3,706 (7.3%)	2,313 (7.9%)	
Laterality			0.001
Left	25,122 (49.2%)	14,137 (48.1%)	
Right	25,905 (50.8%)	15,275 (51.9%)	
Grade			<0.0001
I	4,603 (9.0%)	4,134 (14.0%)	
II	22,715 (44.5%)	15,125 (51.4%)	
III	13,954 (27.3%)	5,601 (19.0%)	
IV	3,386 (6.6%)	455 (1.5%)	
Unknown	6,369 (12.5%)	4,096 (13.9%)	
AJCC T stage			<0.0001
T1	29,842 (58.5%)	27,282 (92.7%)	
T2	8,593 (16.8%)	562 (1.9%)	

T3	12,244 (24.0%)	1,554 (5.3%)
T4	348 (0.7%)	14 (0.0%)
Tumor size	<0.0001	
0.1-4.9	21,450 (42.0%)	25,731 (87.5%)
5.0-9.9	23,181 (45.4%)	3,561 (12.1%)
10.0-14.9	5,360 (10.5%)	120 (0.4%)
15.0-20.0	1,036 (2.0%)	0 (0.0%)

RN: radical nephrectomy; NSS: nephron sparing surgery.

Results

Patient characteristics

A total of 80,439 RCC patients were enrolled in the study, 51,027 (63.4%) of whom received RN and 29,412 (36.6%) of whom received NSS (Table 1). Patients receiving NSS were younger compared to the RN group ($P<0.001$). And no difference in gender between patients receiving RN or NSS ($P=0.156$). As expected, patients who undergo RN surgery have larger tumors ($P<0.0001$) and higher T staging ($P<0.0001$). In addition, patients who underwent RN had tumors with a higher Fuhrman grade ($P<0.0001$).

Impact of surgery type on survival

We grouped patients according to maximum tumor diameter, ranging from 0.1cm to 15cm, and calculated 5 and 10-year OS for different tumor sizes. As shown in figure 1A, with increasing tumor size, the 5-year OS of the patient decreases. When tumor size is less than 8.5 cm, 5-year OS of NSS patients is better than that of patients receiving RN. When the tumor size is more significant than 8.5cm, RN was superior. However, the maximum tumor diameter of 7.2cm is the cutoff for RN and NSS from the perspective of 10-year overall survival (Fig 1B).

Gender and age stratified analysis

We stratified by gender and age to further analyze the prognostic differences between the two surgical approaches. Interestingly, in almost all subgroups, the five-year OS was slightly higher for patients with NSS than for those in the RN group (Fig 2A-2C). Except in elderly patients (≥ 60 years), NSS patients have a superior five-year OS in kidney cancers smaller than 7.2 cm (Fig 2D). While two surgical subgroups of male, female, young and old patients showed differences in 10-year OS when tumors reached 6.4cm, 7.7cm, 7.3cm and 9.2cm in size (Fig 2E- 2H), respectively.

Effect of type of surgery on cardiovascular mortality

Due to the fact that the chronic renal insufficiency increases the risk of cardiovascular events in patients, we further compared the risk of cardiovascular death in patients with the two surgical approaches. As shown in Fig3, cumulative cardiovascular mortality was higher in patients receiving RN than in those receiving NSS in both young and elderly patients. And the risk of cardiovascular death after kidney cancer surgery is both significantly higher in older patients than in younger patients.

Discussion

The choice of RCC surgical procedure requires a balance between the tumor's location and size, the patient's health status, and many other factors. In this study, we provided a new way of determining the surgical approach in tumor size. In general, we found that as tumor size increased, the patients' long-term OS decreased progressively, regardless of the surgical option. However, when the tumor size was less than 7.2 cm, OS was better in patients who received NSS than those who received RN. And when the tumor size was more extensive than 8.5 cm, patients receiving RN showed an advantage in OS. When the tumor was 7.2 cm to 8.5 cm, there was little difference in OS between the two surgical approaches. Besides, stratified analysis by age and sex suggested that the tumor size cutoff applicable to NSS and RN may be around 6-7 cm. Except for young people, whose tumor size thresholds need to be higher.

More than one study has found similar prognostic effects of RN and NSS surgery in patients with localized large RCC(16-19). And these studies further promote aggressive surgical selection strategies for NSS. However, these studies were limited by sample size or stratified patients into simple categories such as T-stage, elderly patients. Besides, few studies have examined the differences between RN and NSS in T2 RCC. Breau et al.(17) reported that the effect of NSS is similar to that of RN in the management of T2 or larger RCC. However, a 13-center study showed NSS surgery is an independent risk factor for patient's outcome in RCC larger than 7 cm ($P = 0.025$)(20). Considering the puzzling role of NSS in large RCC, our study retrospectively included 80,439 patients who received either RN or NSS. Patients were stratified according to tumor size from 0.1cm to 20cm.

In our research, we found patients with RCC smaller than 7.6 cm in size could achieve longer OS through NSS. And this means that patients in stage T1b may be more appropriate for NSS. And this finding is consistent with the recommendations of the latest European Association of Urology (EAU) guidelines on RCC. As mentioned above, studies of T2 RCC reached contradictory conclusions, which may be due to differences in the characteristics of each study's patient populations. Notably, a meta-analysis that included four studies specifically comparing RN and NSS of T2 RCC showed that patients receiving NSS had lower tumor-specific mortality and tumor recurrence rates despite increased blood loss and the likelihood of complications(12). This comprehensive study contradicts our conclusions, which may be because they only included a total of 212 NSSs for T2 RCC. And a well-designed randomized controlled trial is necessarily better to define the role of NSS in larger RCC.

Our study still has some unavoidable limitations. Although 80,439 cases were included in this study, the composition of patients receiving RN and NSS differed in terms of age, Fuhrman grade, T-stage, and other

characteristics, leading to biased analysis. Second, due to the limitations of the retrospective study, it is not possible to consider surgical techniques with more detail, such as subdividing the surgical approach into open, laparoscopic and robotic surgery. Third, due to the limitation of data size, we were unable to accurately describe the trend of CSS in RN and NSS patients. Given that patients with postoperative RCC often lose renal function, decreased renal function is strongly associated with increased all-cause mortality and cardiovascular-related mortality(21,22). Thus, patients receiving either RN or NSS will have higher CSS than OS. And this may partially explain the increase in the applicable tumor size range of the NSS in the CSS scatter plot.

Conclusions

Our retrospective study suggests that RN may remain the preferred approach for larger kidney tumors (>8.5 cm), and NSS may be more recommended for kidney tumors <7.2 cm. And a well-designed randomized controlled trial is necessarily better to define the role of NSS in larger RCC. The growth site of the tumor, the surgeon's experience and so forth are all factors that influence the choice of the surgical method, and the specific surgical procedure still requires a comprehensive judgment.

Abbreviations

RCC: Renal cell carcinoma

RN: Radical nephrectomy

NSS: Nephron sparing surgery

OS: overall survival

SEER: Surveillance, Epidemiology, and End Results database

CSS: Cancer-specific survival

EAU: European Association of Urology

Declarations

Funding

Jiangsu Province TCM Leading Talent Training Project. (No.SLJ0211)

Project of National Clinical Research Base of Traditional Chinese Medicine in Jiangsu Province. (No.JD2019SZXYB04)

Competing Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Ethical Approval and Consent to participate

Ethical approval was not required for this study, because the data used in this study were obtained from the SEER database in a publicly available manner.

Consent for publication

Yes

Availability of supporting data

Not applicable

Author contributions

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(VI) Manuscript writing: All authors

(VII) Final approval of manuscript: All authors

Acknowledgements

Not applicable

Authors' information

Not applicable

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Figures

Figure 1

The five- and ten-year overall survival scatter plot for different tumor sizes. Figure 1A: The five-year overall survival scatter plot for different tumor sizes. Figure 1B: The ten-year overall survival scatter plot for different tumor sizes. The blue line is the scatter plot fitting curve for patients receiving RN, and the red line is the scatter plot fitting curve for patients receiving NSS. RN: radical nephrectomy, NSS: nephron sparing surgery.

Figure 2

The five- and ten-year overall survival scatter plot for different tumor sizes by gender and age stratified analysis. Figure 2A-2D: The five-year overall survival scatter plot for different tumor sizes of male, female, young and old patients. Figure 2E-2H: The ten-year overall survival scatter plot for different tumor sizes of male, female, young and old patients. The blue line is the scatter plot fitting curve for patients receiving RN, and the red line is the scatter plot fitting curve for patients receiving NSS. RN: radical nephrectomy, NSS: nephron sparing surgery.

Figure 3

The Cumulative risk of cardiovascular death. The cumulative risk of cardiovascular death of young and old patients receiving RN or NSS. RN: radical nephrectomy, NSS: nephron sparing surgery.