ORIGINAL RESEARCH

The Effect of Cytoreductive Partial Nephrectomy in Elderly Patients with Metastatic Renal Cell Carcinoma

Jiabi Chen
Qingliu He
Weihui Liu
Yining Li
Wei Zhuang (ID)

Department of Urology, The Second Affiliated Hospital of Fujian Medical University, Quanzhou, Fujian, People's Republic of China

Objective: To explore the survival value of cytoreductive partial nephrectomy (cPN) in elderly with metastatic renal cell carcinoma (EmRCC) and evaluate the characteristics of patients who benefit from cPN.

Materials and Methods: This was a study including 6105 patients aged ≥65 years with metastatic renal cell carcinoma (RCC) queried from Surveillance, Epidemiology and End Results (SEER) database between 2010 and 2015, among which 1264 patients underwent cytoreductive nephrectomy (CN), 78 patients underwent cPN and 1186 patients underwent cytoreductive radical nephrectomy (cRN). Kaplan–Meier (K-M) method and Cox proportional-hazards model (COX) were used to evaluate the survival prognosis. Overall survival (OS) was compared between groups using propensity score matching (PSM) to balance the effects of confounding factors such as general features and pathological features. At last, we constructed a nomogram visualization modelled by R language to predict survival.

Results: For patients with EmRCC, especially for male patients with tumors size ≤7 cm, N0 stage, or isolated metastases, cPN brought a better survival than cRN. Tumor size and N stage were independent risk factors affecting the survival of cPN patients. cPN for patients with tumor size >7 cm or N1 stage may present a higher risk of death.

Conclusion: The implementation of cPN for patients with EmRCC who meet specific clinical characteristics such as tumors size ≤7 cm, N0 stage, or isolated metastases seems to help improve the survival prognosis.

Keywords: elderly, metastatic renal cell carcinoma, partial nephrectomy, radical nephrectomy, survival

Introduction

With the aggravation of global aging, the proportion of the elderly patients with renal cell carcinoma (RCC) is increasing.[1] Authoritative guide provides a lot of guidelines for the management of patients with RCC, but the recommended treatment for elderly patients is often the same as that for young people, ignoring the elderly with low glomerular filtration rate baseline, high proportion of cardiovascular disease and low drug toxicity tolerance. It requires to strengthen the individualized guidance for this part of patients.

The release of CARMENA trial results challenged the role of cytoreductive nephrectomy (CN) in metastatic RCC (mRCC).[2] But it is undeniable that the trial has been criticized for some selection bias (a slow and incomplete recruitment, incorporating too many high-transfer cases and patients with poor prognosis).[3,4]

Correspondence: Wei Zhuang
The Second Affiliated Hospital of Fujian Medical University, Zhongshan North Road, Licheng District, Quanzhou, Fujian 362000, People's Republic of China
Fax +86 59 587365269
Email lx2998121314@163.com

Therefore, the trial could not reduce the value of CN in intermediate-risk patients with mRCC.[5,6]

Cytoreductive radical nephrectomy (cRN) and cytoreductive partial nephrectomy (cPN) are two major surgical methods of CN, and the application of cPN in mRCC has been increasing in recent years.[7] It is generally believed that compared with cRN, cPN can not only reduce tumor burden equally,[8] but also better protect renal function, reduce the occurrence of long-term cardiovascular diseases, and increase patients' tolerance to systemic therapy drugs, which is conducive to long-term survival.[9,10] However, the risks of increased perioperative complications and prolonged operative time are disturbing equally. Elderly metastatic renal cancer (EmRCC) is often considered to have a worse long-term survival and lower resistance to surgical risks; hence, it is directly abandoned for surgery or rarely considered for cPN treatment.[11]

To the best of our knowledge, there lacks a systematic prospective study on the treatment of EmRCC population, and the retrospective analysis of single center often has the defect of a small number of cases.[12] Based on the extensive representation of SEER database, this study attempts to explore the value of cPN in EmRCC from the perspective of population epidemiology beyond clinical trials.

Materials and Methods

Patients aged ≥65 were defined as the elderly,[1,12] and EmRCC population was queried from SEER database between 2010 and 2015, eliminating patients diagnosed with "autopsy" or "death certificate", "source information unknown" and "incomplete follow-up information".

Cell classification was performed according to Fuhrman grade and TNM staging was conducted according to AJCC 2007th edition. Histologic type was divided into two categories: "clear cell renal cell carcinoma (ccRCC)" and "other". According to the metastasis of liver, lung, bone and brain, metastasis sites were divided into two parts: "isolated site group" and "multiple sides group".

With the help of IBM SPSS Statistics 24.0 software, Kaplan–Meier (K-M) method was applied to perform single-factor survival analysis of variables, and selected variables with $P<0.05$ into the Cox regression model to evaluate independent risk factors for overall survival (OS). OS was compared between cPN group and the cRN group using propensity score matching (PSM) to balance the effects of confounding factors such as general features and pathological features.[13] The nomogram model was constructed using R language (version 3.5.1; R Foundation; Foreign package,

survival package and rms package) to estimate the survival rate which performed the internal verification.[14] A $P<0.05$ was considered statistically significant.

Results

A total of 6105 patients were identified with EmRCC who met the inclusion criteria. Only 1542 (25.3%) patients received surgical treatment, among which 78 patients with "bilateral tumor, tumor biopsy or focal lesion only, and unclear CN mode" were excluded. Hence, a total of 1264 patients undergoing CN (78 cases of cPN and 1186 cases of cRN) were included in the final analysis. The baselines of cPN and cRN were significantly different in tumor size and T stage. After PSM analysis (matching tolerance 0.02), the remaining 59 cases of cPN and 149 cases of cRN matched well with clinicopathological features. More detailed demographic and clinical information are presented in Table 1.

Among EmRCC cohort, the media survival time (MST) of patients undergoing CN was 19.00 months (95% CI, 16.83–21.17), which was significantly longer than that of patients who were not treated with surgery (MST, 3.00 months; 95% CI, 2.81–3.19) (P<0.001). Patients who received cRN were associated with worse survival than those having cPN (cPN: MST, 32.00months; 95% CI, 8.11–55.89 vs cRN: MST, 19.00months; 95% CI, 16.66–21.34; P=0.011). After PSM analysis, the survival advantage of patients having cPN was still obvious (cPN: MST, 32.00months; 95% CI, 12.58–51.42 vs cRN: MST, 19.00months; 95% CI, 13.05–24.95; P=0.042) (Figure 1).

Analysis of each subgroup showed that OS and CSS of cPN were superior to cRN in male patients with tumor size ≤7 cm, N0 stage or isolated metastasis and the difference was statistically significant (Table 2). The effect of cPN in N1 stage patients was worse than that of cRN (cPN: MST, 7.17 months; 95% CI, 3.80–10.53 vs cRN: MST, 16.32 months; 95% CI, 13.90–18.75; P=0.026) (Figure 2).

Variables with P<0.05 in K-M analysis were selected into COX multivariate analysis (Follow LR method) and we found that tumor size and N stage were independent risk factors affecting the survival of patients with EmRCC who underwent cPN. (Table 3). The risk of death in patients with tumor >7 cm was 2.54 times than that of patients with tumor ≤7 cm (95% CI, 1.25–5.13; P=0.010). The risk of death in N1 patients was 5.48 times than that of N0 patients (95% CI, 2.46–12.22; P<0.001). (Figure 3)

On the Cox regression model, gender, T stage, N stage, CN and distant metastasis were independent predictors

Table 1 The Portion and Distribution of Clinical Features of Elderly Patients with Metastatic Renal Cell Carcinoma Before and After Propensity Matching

Variable	Before PSM (n=1264)			After PSM (n=208)		
	PN (n=78, %)	RN (n=1186, %)	*p*-value	PN (n=59, %)	RN (n=149, %)	*p*-value
Age at diagnosis, years	71.59 ± 5.22	72.11 ± 5.57	0.425	71.39 ± 5.04	72.34 ± 5.93	0.278
Race			0.264			0.067
Black	7 (9.0%)	63 (5.3%)		6 (10.2%)	4 (2.7%)	
White	68 (87.2%)	1043 (87.9%)		51 (86.4%)	132 (88.6%)	
Other[a]	3 (3.8%)	80 (6.7%)		2 (3.4%)	13 (8.7%)	
Gender			0.325			0.411
Male	56 (71.8%)	784 (66.1%)		43 (72.9%)	98 (65.8%)	
Female	22 (28.2%)	402 (33.9%)		16 (27.1%)	51 (34.2%)	
Marital Status			0.786			0.354
Single[b]	20 (25.6%)	346 (29.2%)		14 (23.7%)	49 (32.9%)	
Married	56 (71.8%)	799 (67.4%)		43 (72.9%)	97 (65.1%)	
Unknown	2 (2.6%)	41 (3.5%)		2 (3.4%)	3 (2.0%)	
Insurance Status			1.000			1.000
Insured	78 (100.0%)	1166 (98.3%)		59 (100.0%)	147 (98.7%)	
Uninsured	0 (0.0%)	8 (0.7%)		0 (0.0%)	1 (0.7%)	
Unknown	0 (0.0%)	12 (1.0%)		0 (0.0%)	1 (0.7%)	
Site			1.000			0.645
Right	36 (46.2%)	551 (46.5%)		27 (45.8%)	75 (46.2%)	
Left	42 (53.8%)	634 (53.5%)		32 (54.2%)	74 (49.7%)	
Unknown	0 (0.0%)	1 (0.1%)		0 (0.0%)	0 (0.0%)	
Histologic Type			0.055			0.417
ccRCC	61 (78.2%)	894 (75.4%)		47 (79.7%)	112 (75.2%)	
pRCC	11 (14.1%)	72 (6.1%)		7 (11.9%)	12 (8.1%)	
chRCC	0 (0.0%)	14 (1.2%)		0 (0.0%)	0 (0.0%)	
CDC	0 (0.0%)	10 (0.8%)		0 (0.0%)	1 (0.7%)	
SRCC	3 (3.8%)	72 (6.1%)		3 (5.1%)	8 (5.4%)	
Other	3 (3.8%)	124 (10.5%)		2 (3.4%)	16 (10.7%)	
Tumor Size, cm			< 0.001			0.431
≤4	29 (37.2%)	74 (6.2%)		13 (22.0%)	20 (13.4%)	
4–7	23 (29.5%)	319 (26.9%)		20 (33.9%)	61 (40.9%)	
> 7	25 (32.1%)	781 (65.9%)		25 (42.4%)	65 (43.6%)	
Unknown	1 (1.3%)	12 (1.0%)		1 (1.7%)	3 (2.0%)	
Fuhrman Grade			0.607			0.925
Grade 1	1 (1.3%)	13 (1.1%)		1 (1.7%)	3 (2.0%)	
Grade 2	18 (23.1%)	207 (17.5%)		13 (22.0%)	30 (20.1%)	
Grade 3	25 (32.1%)	417 (35.2%)		19 (32.2%)	56 (37.6%)	
Grade 4	22 (28.2%)	387 (32.6%)		19 (32.2%)	40 (26.8%)	
Unknown	12 (15.4%)	162 (13.7%)		7 (11.9%)	20 (13.4%)	
T Stage			< 0.001			0.090
T1	41 (52.6%)	147 (12.4%)		22 (37.3%)	46 (30.9%)	
T2	9 (11.5%)	134 (11.3%)		9 (15.3%)	14 (9.4%)	
T3	20 (25.6%)	772 (65.1%)		20 (33.9%)	77 (51.7%)	
T4	8 (10.3%)	125 (10.5%)		8 (13.6%)	10 (6.7%)	
Unknown	0 (0.0%)	8 (0.7%)		0 (0.0%)	2 (1.3%)	

(*Continued*)

Table 1 (Continued).

Variable	Before PSM (n=1264)			After PSM (n=208)		
	PN (n=78, %)	RN (n=1186, %)	*p*-value	PN (n=59, %)	RN (n=149, %)	*p*-value
N Stage			0.115			1.000
N0	63 (80.8%)	840 (70.8%)		47 (79.7%)	116 (77.9%)	
N1	12 (15.4%)	302 (25.5%)		10 (16.9%)	27 (18.1%)	
Unknown	3 (3.8%)	44 (3.7%)		2 (3.4%)	6 (4.0%)	
Metastasis Sites			0.516			0.406
One Site	65 (83.3%)	967 (81.5%)		49 (83.1%)	118 (79.2%)	
Two Sites	10 (12.8%)	191 (16.1%)		7 (11.9%)	27 (18.1%)	
≥Three Sites	3 (3.8%)	28 (2.4%)		3 (5.1%)	4 (2.7%)	

Notes: [a]Other: American Indian/AK Native, Asian/Pacific Islander and other races; [b]Single: Never married, Domestic Partner, Widowed, Separated or Divorced.
Abbreviations: PSM, Propensity Score Matching; PN, Partial Nephrectomy; RN, Radical Nephrectomy; ccRCC, Clear Cell Renal Cell Carcinoma; pRCC, Papillary Renal Cell Carcinoma; chRCC, Chromophobe Renal Cell Carcinoma; CDC, Collecting Duct Carcinoma; sRCC, Sarcomatoid Renal Cell Carcinoma.

affecting the OS of patients with EmRCC. The nomogram model was established based on statistical results and clinical experience to predict the 1-year, 2-year and 3-year estimated survival rate of patients with EmRCC. The c-index of the model was 0.647 (95% CI, 0.637–0.657; P<0.01). (Figure 4)

Discussion

With the progress of global aging, the number of elderly patients in metastatic renal cancer is increasing. Older patients have many characteristics of their own, such as visceral reserve dysfunction, more toxic side effects and poorer tolerance on drug treatment, as well as shorter natural lifespan, seemingly unable to enjoy the benefits of long-term survival of cPN.[1] Although authoritative guidelines have various norms for the treatment of RCC, they often confuse the elderly with the young patients, which lack particular personalized guidance for the elderly. To the best of our knowledge, this is the first study focusing on the survival of patients with EmRCC undergoing cPN. We found that the MST of cPN is superior to cRN among patients with EmRCC, especially in males, tumor size ≤7 cm, N0 stage or isolated metastasis. Tumor size and N stage were independent risk factors affecting the survival of patients who underwent cPN. Furthermore, we established the first nomogram model including CN information to predict the survival rate of patients with EmRCC.

The release of CARMENA trial has weakened the value of CN in the age of vascular targeted therapy.[2] However, due to the limitations of patient selection bias in this trial and considering that some patients lack a good economic basis to bear the high cost of vase-targeted drugs, CN still has a unique position in the treatment of metastatic renal cancer.[3–5] In recent
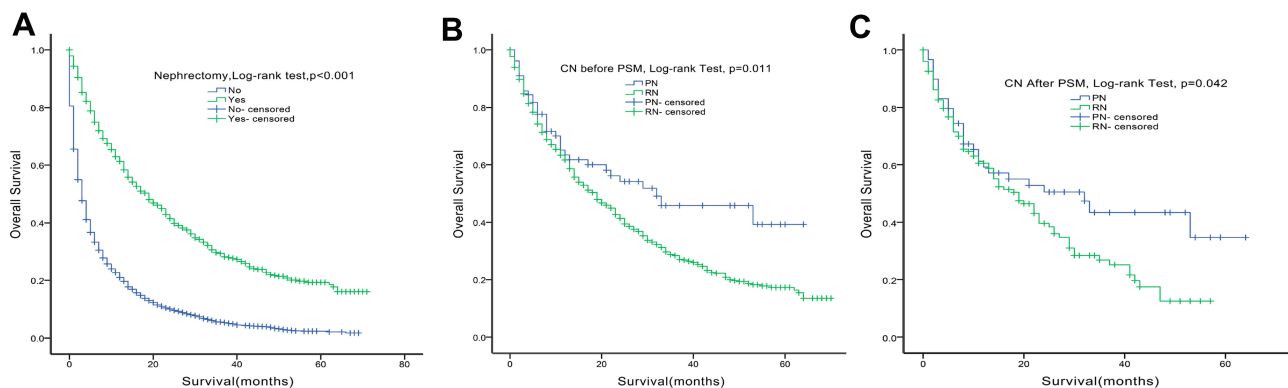

Figure 1 Kaplan–Meier curves of overall survival for elderly metastatic renal cell carcinoma according to cytoreductive nephrectomy (**A**), partial nephrectomy and radical nephrectomy (**B, C**).

Table 2 Survival Comparison of PN and RN Among Different Subgroups of Elderly Metastatic Renal Cell Carcinoma

Variable	Mean Survival Time of OS, Months (95% CI)		p-value	Mean Survival Time of CSS, Months (95% CI)		p-value
	PN (n=78)	RN (n=1186)		PN (n=78)	RN (n=1186)	
Gender						
Male	35.30 (27.62–42.98)	27.35 (25.30–29.41)	0.032	42.29 (34.51–50.07)	34.07 (31.63–36.51)	0.036
Female	30.13 (19.70–40.55)	2.22 (21.73–26.71)	0.263	33.78 (23.18–44.38)	29.92 (26.89–32.95)	0.351
Histologic Type						
ccRCC	36.77 (29.30–44.25)	29.46 (27.56–31.36)	0.059	41.37 (33.77–48.97)	35.85 (33.62–38.08)	0.129
Other	27.31 (13.53–41.09)	16.29 (13.69–18.90)	0.067	39.54 (24.41–54.67)	22.00 (18.51–25.49)	0.038
Tumor Size, cm						
≤7	43.39 (35.37–51.42)	28.49 (25.68–31.30)	0.002	48.34 (40.57–56.12)	35.10 (31.78–38.42)	0.006
> 7	18.95 (10.87–27.02)	24.96 (23.02–26.90)	0.410	26.00 (35.90–56.87)	31.15 (28.80–33.50)	0.606
Grade						
G1-2	42.04 (30.43–53.66)	37.01 (33.15–40.88)	0.227	52.98 (43.80–62.16)	44.14 (39.93–48.36)	0.067
G3-4	31.93 (23.19–40.68)	22.75 (20.91–24.59)	0.061	37.66 (28.45–46.87)	28.89 (26.57–31.22)	0.085
T Stage						
T1	41.83 (33.48–50.18)	33.18 (28.31–38.04)	0.086	48.16 (40.49–55.83)	39.52 (34.02–45.01)	0.050
T2	32.30 (18.22–46.39)	31.83 (26.99–36.68)	0.479	36.47 (22.42–50.51)	39.48 (34.13–44.84)	0.659
T3	24.13 (13.93–34.32)	25.16 (23.22–27.10)	0.811	28.75 (17.46–40.03)	31.23 (28.87–33.59)	0.852
T4	18.88 (0.7337.02)	17.31 (13.42–21.20)	0.927	25.62 (5.01–46.24)	23.41 (18.03–28.78)	0.722
N Stage						
N0	42.11 (34.83–49.40)	29.97 (27.98–31.96)	0.002	47.86 (40.81–54.90)	36.35 (34.03–38.67)	0.003
N1	7.17 (3.80–10.53)	16.32 (13.90–18.75)	0.026	9.64 (4.43–14.85)	22.04 (18.65–25.42)	0.048
Number of Metastasis Sites						
One	37.80 (30.50–45.11)	28.36 (26.51–30.20)	0.011	44.61 (37.26–51.96)	34.90 (32.73–37.08)	0.009
≥Two	20.39 (7.96–32.81)	17.28 (14.54–20.01)	0.664	23.50 (10.12–36.88)	22.26 (18.63–25.89)	0.993

Abbreviations: OS, Overall Survival; CSS, Cancer-Specific Survival; 95% CI, 95% Confidence Interval; PN, Partial Nephrectomy; RN, Radical Nephrectomy; ccRCC, Clear cell Renal cell carcinoma.

years, cPN has replaced cRN in the treatment of RCC with tumor size ≤4 cm, becoming the gold standard for surgical treatment. Even in tumor size >7 cm of RCC, some scholars have tried PN to achieve clinical efficacy comparable to RN.[15] Due to poorer baseline kidney function in elderly patients, PN can bring better long-term renal function protection,[10,16] which not only reduces the risk of chronic kidney disease (CKD) progression and the incidence of cardiovascular events,[8,17] but also enable patients to better tolerate the toxic side effects of systemic drug therapy such as vascular targeted therapy, immunotherapy, and thus may have better prospects in metastatic RCC.[18]

Our study found that the long-term survival of surgically treated patients with EmRCC was better than that of non-surgical patients, which was consistent with other research results.[19–21] Moreover, all the subjects were patients with EmRCC who underwent CN in SEER database, which

greatly reduced the selection bias of retrospective data and increased the accuracy of conclusions. Whether before or after PSM pairing, the OS of patients undergoing cPN has certain advantages over those undergoing cRN, suggesting that we should pay attention to the selection of surgical methods when patients with EmRCC are treated with CN.

Disputes over cPN procedures often lie in complications and duration of surgery, which may be one of the reasons for the lower proportion of cPN in patients with EmRCC. However, with improvements of anesthesia, surgical techniques and equipment, the gap between the age and surgical methods of complications has become smaller.[22] The cPN treatment does not increase the incidence and mortality of perioperative complications in patients with EmRCC.[16,23,24]

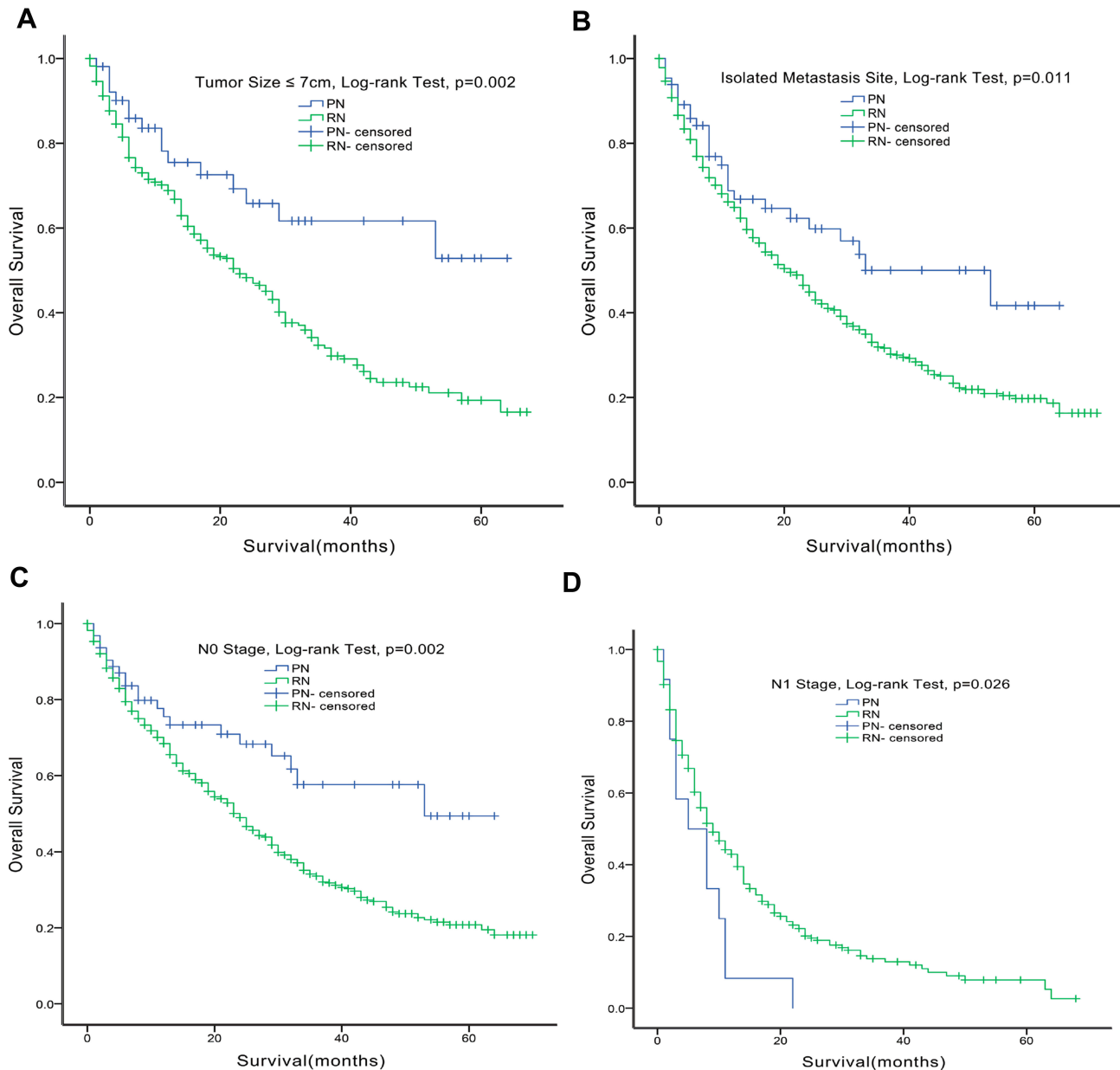Further subgroup analysis showed that in male patients with EmRCC, tumor size ≤7 cm, N0 stage and isolated

Figure 2 Survival comparison of patients undergoing cytoreductive nephrectomy according to tumor size ≤7cm (**A**), isolated metastasis (**B**) and N0 stage (**C**) and N1 stage (**D**).

distant metastasis, cPN would bring a more significant survival advantage than cRN. For patients with EmRCC with the above clinical characteristics, more attention should be paid to cPN rather than just considering cRN for the purpose of reducing tumor burden, improving clinical symptoms and prolonging long-term survival. This is the most recent conclusion to our knowledge about the therapeutic value of cPN in EmRCC. This challenges the conventional notion among many clinicians that patients with EmRCC have worse survival duration and cPN brings higher surgical risk surgery and fewer

benefit.[11] For such patients (male, tumor size ≤7 cm, N0 stage and isolated distant metastasis), cPN treatment can be actively considered.

COX multivariate analysis of patients undergoing cPN indicated that the risk of death in patients with tumor >7 cm was 2.54 times more than that of patients with tumor ≤7 cm and the risk of death in N1 patients was 5.48 times more than that of N0 patients. This suggests that cPN is more desirable for patients with EmRCC with a small primary tumor volume or N0 stage. The survival benefits of CN were underestimated for limitations of

Table 3 Multivariate Cox Regression Analyses of Prognostic Factors Influencing the Overall Survival of Elderly Patients with Metastatic Renal Cell Carcinoma Who Were Treated with Partial Nephrectomy. (Step 2, Follow LR)

Variable	Univariate Analyses		Multivariate Analyses	
	Log-Rank (χ^2)	p-value	HR (95% CI)	p-value
Age at diagnosis	0.70	0.402	-	-
Race	4.66	0.097	-	-
Gender	0.04	0.849	-	-
Marital status	4.02	0.134	-	-
Site	0.03	0.871	-	-
Histologic type	1.12	0.290	-	-
Tumor Size	12.18	<0.001	-	-
≤7 cm	-	-	Reference	1.000
>7 cm	-	-	2.54(1.25–5.13)	0.010
Fuhrman grade	9.44	0.024	-	-
T stage	10.02	0.018	-	-
N Stage	30.78	<0.001	-	<0.001
N0	-	-	Reference	1.000
N1	-	-	5.48(2.46–12.22)	<0.001
Unknown	-	-	2.51(0.58–10.94)	0.219
Metastasis sites	5.00	0.025	-	-

Abbreviations: HR, Hazard Ratio; 95% CI, 95% Confidence Interval.

CARMENA trial (incorporating too many high-transfer cases and patients with poor prognosis).[3,4] The results of multivariate analysis facilitated our selection of patients with EmRCC that may benefit more from cPN clinically. The cPN is not recommended for patients with EmRCC who were diagnosed with large primary tumors or lymph node involvement confirmed by clinical imaging.

The constructed nomogram model has a certain predictive value for survival rates of patients with EmRCC. Although the internal validation C-index was not perfect, the model showed that cPN treatment in specific patients with EmRCC (male, T1, N0, isolated metastases) may have superior 1-, 2-, and 3-year survival rate. Among the EmRCC population conformed to the above clinical feature, cPN therapy should be fully considered for a patient with a good physical function.

As with any study utilizing the SEER database, retrospective analyses have certain limitations. For example, there is a lack of physical function scores such as Karnofsky score or ECOG score and other key data such as co-morbid conditions, as well as information related to simultaneous or subsequent targeted vascular therapy and immunotherapy, which makes our conclusion biased to some extent. However, due to the lack of large-scale prospective studies for CN treatment in EmRCC population, this is the largest known study of a rare group of patients with EmRCC from a large epidemiological database. We anticipate that this work will be helpful for patient counseling and for modifying future exclusion criteria in clinical trials.

Conclusion

In our study, we found that: 1. In EmRCC, the MST of cPN seems to be superior to cRN, especially for males, tumor size ≤7 cm, N0 stage or isolated metastasis. 2. Tumor size and N stage were independent risk factors affecting the survival of patients who underwent cPN,
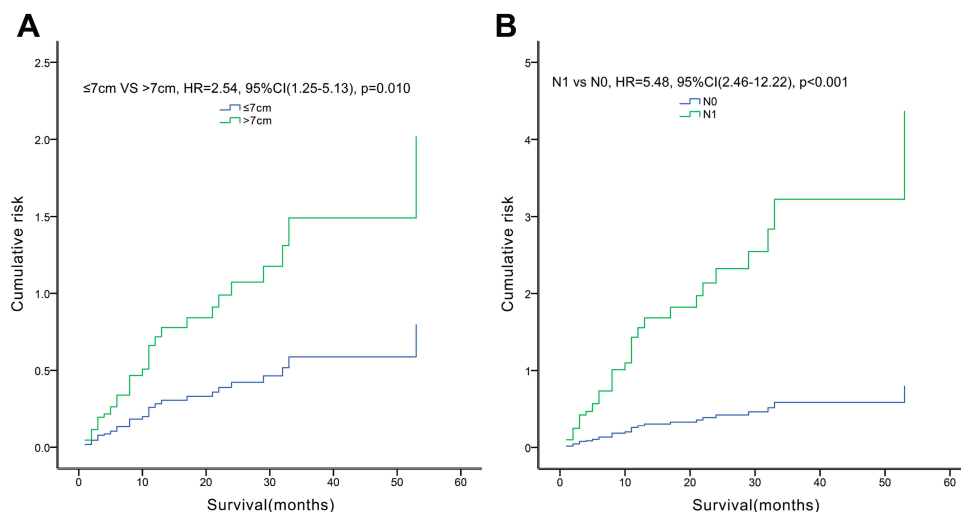

Figure 3 Risk analysis of patients undergoing cytoreductive partial nephrectomy according to tumor diameter >7cm (**A**) and N1 stage (**B**).
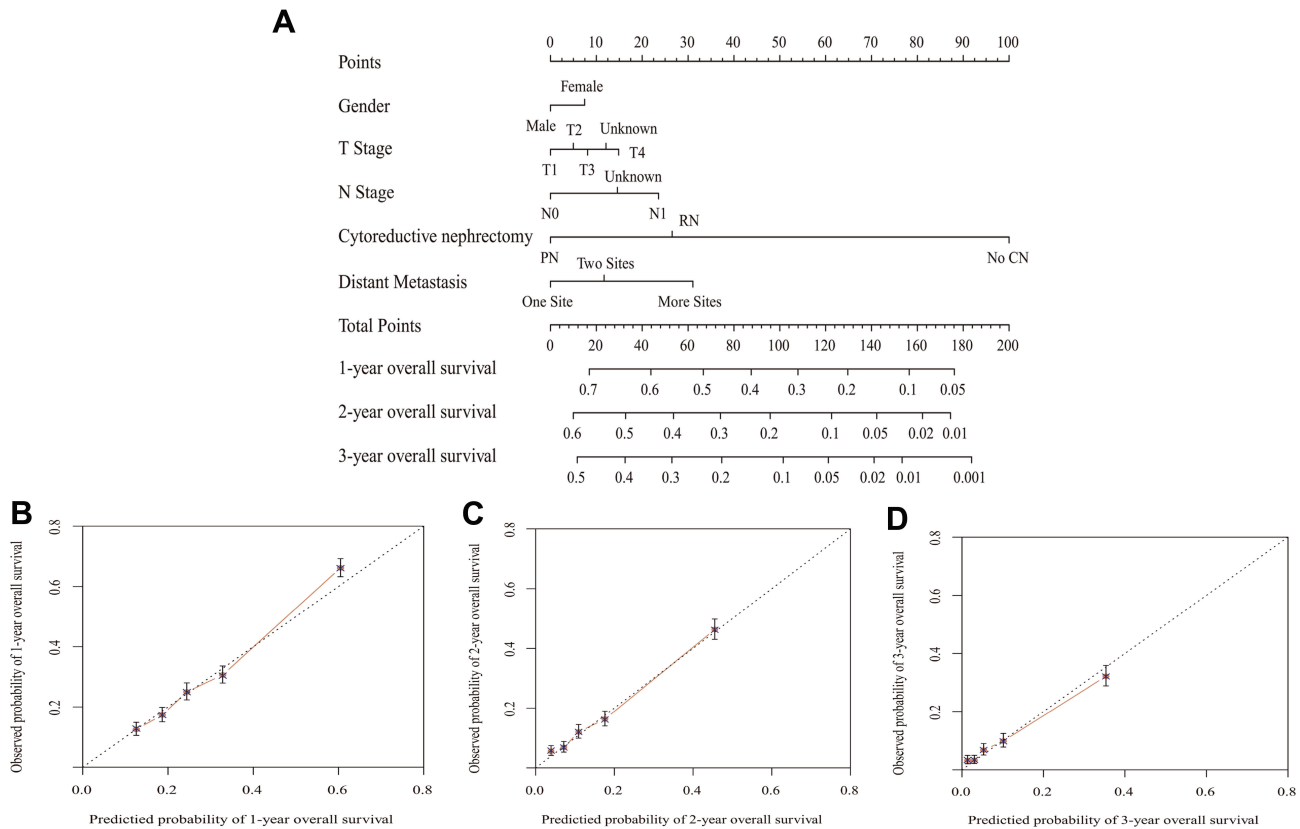
Figure 4 Nomogram model (**A**) for elderly metastatic renal cell carcinoma and calibration curve of survival probability prediction: 1-year (**B**), 2-year (**C**), 3-year (**D**).

while cPN among patients with tumor size >7 cm or N1 stage may bring a higher risk.

Compliance with Ethical Standards

All procedures performed in studies involving human participants conform to the standards of the institutional and national ethics committees, as well as to the 1964 Helsinki Declaration and subsequent relevant ethics. We obtained the authorization to access the SEER database, with the number 14,260-Nov2016. Patient-informed consent is not required to extract data from the SEER database.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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