



Do renal cell carcinoma patients with brain metastases still need nephrectomy?

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Abstract

Purpose To evaluate the value of nephrectomy for survival prognosis in renal cell carcinoma (RCC) patients with brain metastases (BM).

Methods There were 933 RCC patients diagnosed with BM in SEER database from 2010 to 2014. Kaplan–Meier method and Cox regression model were used to analyze the survival prognosis. The effect of nephrectomy on overall survival (OS) was analyzed by propensity score matching. The competitive risk model was performed to explore the relationship between surgery and cancer-specific survival (CSS), and the nomogram visualization model was established by R language to predict survival rate.

Results BM accounted for 1.5% of newly diagnosed RCC patients and 11.1% of M1 stage patients with the median survival time of 5 months (95% CI 4.5–5.5). Age 45–65 years, tumor diameter > 10 cm and histologic type of clear cell renal cell carcinoma (ccRCC) were high risk factors for BM in RCC patients. Age, N stage, lung metastasis and nephrectomy were independent prognostic factors. Nephrectomy was beneficial for both OS and CSS for the analysis of 216 patients successfully matched. The nomogram model has a certain value in predicting the survival rate with the internal verification *c*-index of 0.727.

Conclusions Patients with high risk of BM (age 45–65 years, tumor diameter > 10 cm, histologic type of ccRCC) should emphasize brain imaging screening during follow-up. Nephrectomy may bring survival advantages for RCC patients with BM. Nomogram model based on nephrectomy can help predicting the 1-, 2- and 3-year survival rates.

Keywords Brain metastases · Renal cell carcinoma · Nephrectomy · Epidemiology · Survival

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Introduction

Renal cell carcinoma (RCC) is one of the common sources of brain metastases (BM), and the incidence is second only to lung cancer, which is similar to breast cancer and melanoma [1, 2]. BM is a serious stage in the development of RCC, which has a high mortality and seriously affects the prognosis of patients [1, 3]. However, due to the limitation of fewer patients, there is little research on the prognostic effect of RCC patients with BM.

In recent years, the discovery of a variety of new monoclonal antibodies against circulating VEGF, mTOR inhibitors-targeted therapy, and PD-1 and PD-L1 immunotherapy drugs have provided more choices for advanced RCC patients, bringing a significant improvement in survival [4–6]. There lacks epidemiological data to confirm whether traditional nephrectomy is still necessary for RCC patients

with BM to improve the survival in the new period of systemic therapy [3, 7].

The Surveillance, Epidemiology and End Results (SEER) database was provided by the American National Cancer Institute. It contains clinical and pathological data of cancer patients from 19 regional areas in the USA, whose results are highly representative [1, 8]. The database has clearly coded the BM status of malignant tumors since 2010 [CS mets at DX-brain (2010+)], and there are specific codes for surgical procedures such as partial nephrectomy and radical nephrectomy [RX Summ-Surg Prim Site (1998+)].

The paper attempted to analyze the survival of newly diagnosed RCC patients with BM in the SEER database from 2010 to 2014. Among the prognostic factors, we especially analyzed the data after propensity score matching (PSM) to explore the value of nephrectomy on overall survival (OS) and cancer-specific survival (CSS), and established a survival prediction visualization model.

Methods

There were 933 RCC patients diagnosed with BM, eliminating patients diagnosed of “autopsy” or “death certificate”, “source information unknown”, “incomplete follow-up information” and “local tumor destruction with unknown surgical methods or only freezing, ablation, etc.” in the SEER database between 2010 and 2014. Among the cohort, 221 patients had nephrectomy and 712 patients were not treated with surgery.

According to the age at diagnosis, patients were divided into three groups: “<45 years old”, “45–65 years old” and “>65 years old”. According to the race, they were divided into four groups: “white”, “black”, “other” (including American Indian, Alaska Native, Asian, Pacific Islander) and “unknown”. Marital status was divided into three groups: “unmarried” [including “single (never married)” and “unmarried or domestic partner”], “married” [including “married (including common law)”, “widowed”, “separated” and “divorced”] and “unknown”. Insurance status was divided into three categories: “insured”, “uninsured” and “unknown”. Histologic type was divided into five kinds according to ICD-O-3 standard: “clear cell renal cell carcinoma (ccRCC)”, “papillary renal cell carcinoma (pRCC)”, “chromophobe renal cell carcinoma (chRCC)”, “collecting duct carcinoma (CDC)” and “sarcomatoid renal cell carcinoma (sRCC)” and “other”. Cell classification was performed according to Fuhrman grade and TNM staging was conducted according to AJCC 2007th edition. Surgical condition was classified into two categories: “nephrectomy group” and “non-nephrectomy group”. Nephrectomy group included patients who had undergone surgical procedures such as

partial nephrectomy and radical nephrectomy. Distant metastatic sites included liver, lung, bone and brain.

With the help of IBM SPSS Statistics 24.0 software, we used the Kaplan–Meier (K–M) method to perform single-factor survival analysis of variables such as age, race, marital status, TN stage, Fuhrman grade and nephrectomy, and screened variables with $P < 0.1$ into Cox analysis to evaluate independent risk factors for OS of patients. The Nomogram visualization model was constructed to predict the individual survival rate of patients at 1 year, 2 years and 3 years by R language (version 3.5.1; R Foundation; Foreign package, survival package and RMS package) [9], and the model was internally verified. With the help of SPSS 24.0, SPSS Statistics Essentials for R, psmatching 3.04 spe and R 3.5.1, propensity score matching (PSM) (1:1 matching, matching tolerance 0.1) was performed to balance the effects of confounding factors such as patients’ general features and pathological features, and to compare the difference of OS between the nephrectomy group and non-nephrectomy group [10]. The effect of nephrectomy on CSS was analyzed by means of the competitive risk model of R language (Foreign package, survival package and CMPRSK package) [11].

Results

Risk factors for brain metastasis

From 2010 to 2014, there were 63,807 newly diagnosed RCC patients and 8413 M1 stage patients. Among the patients, 933 cases were diagnosed with BM, accounting for 1.5% of all patients and 11.1% of M1 stage patients, which includes 843 cases of ccRCC (90.4%) with the largest proportion and 2 cases of CDC (0.2%) with the smallest proportion. SRCC is a special subtype of RCC with low incidence and poor prognosis, which can be derived from any type. Therefore, we calculated it in combination with CDC, which has the same poor prognosis and few cases. The other type group included 24 cases (Other, 2.6%), such as neuroendocrine carcinoma, mixed subtype adenocarcinoma and unclassified adenocarcinoma. Among the cohort, 221 patients had nephrectomy and 712 patients were not treated with surgery.

On multivariate logistic regression (Table 1) among RCC patients, age 45–65 years ($P < 0.001$, $Ex(B)$ 1.737), tumor diameter > 10 cm ($P = 0.007$, $Ex(B)$ 1.492) and ccRCC ($P = 0.024$, $Ex(B)$ 1.617) were associated with significantly greater odds of having BM at diagnosis. pRCC ($P = 0.023$, $Ex(B)$ 0.510), chRCC ($P = 0.042$, $Ex(B)$ 0.389), tumor diameter ≤ 4 cm ($P < 0.001$, $Ex(B)$ 0.361), T1 stage ($P < 0.001$, $Ex(B)$ 0.273), T3 stage ($P < 0.001$, $Ex(B)$ 0.597) and N0 stage ($P < 0.001$, $Ex(B)$ 0.451) were associated with marginally lower odds of BM at diagnosis.

Table 1 Incidence proportion and median survival and multivariate logistic analysis of patients with brain metastases in renal cell carcinoma

Variable	Multivariate logistic analysis				Median survival time, months (95% CI)
	With BM (<i>n</i> =933, %)	All RCC (<i>n</i> =63,807, %)	<i>P</i>	Exp(<i>B</i>)	
Age, years					
<45	34 (3.6%)	5520 (8.7%)	0.184	0.780	7.0 (0.7–13.3)
45–65	558 (59.8%)	31,005 (48.6%)	<0.001	1.737	6.0 (5.4–6.6)
>65	341 (36.5%)	27,282 (42.8%)	NA	NA	4.0 (3.5–4.5)
Race					
Black	61 (6.5%)	7840 (12.3%)	0.755	0.829	4.0 (2.1–5.9)
White	798 (85.5%)	51,567 (80.8%)	0.445	1.567	5.0 (4.5–5.5)
Other	71 (7.6%)	3883 (6.1%)	0.343	1.765	5.0 (4.0–6.0)
Unknown	3 (0.3%)	517 (0.8%)	NA	NA	NA
Gender					
Male	643 (68.9%)	41,148 (64.5%)	0.707	1.028	5.0 (4.5–5.5)
Female	290 (31.1%)	22,659 (35.5%)	NA	NA	6.0 (4.8–7.2)
Marital status					
Unmarried	184 (19.7%)	9884 (15.5%)	<0.001	2.609	4.0 (2.9–5.1)
Married	726 (77.8%)	50,127 (78.6%)	<0.001	2.170	5.0 (4.5–5.5)
Unknown	23 (2.5%)	3796 (5.9%)	NA	NA	6.0 (0.0–14.5)
Insurance status					
Insured	868 (93.0%)	60,506 (94.8%)	0.010	2.433	5.0 (4.5–5.5)
Uninsured	54 (5.8%)	1882 (2.9%)	0.046	1.877	5.0 (3.1–7.0)
Unknown	11 (1.2%)	1419 (2.2%)	NA	NA	4.0 (2.5–5.5)
Histologic type					
ccRCC	843 (90.4%)	50,194 (78.7%)	0.024	1.617	5.0 (4.5–5.5)
pRCC	24 (2.6%)	7674 (12.0%)	0.023	0.510	11.0 (7.1–14.9)
chRCC	6 (0.6%)	3172 (5.0%)	0.042	0.389	4.0 (1.9–6.1)
sRCC/CDC	36 (3.9%)	854 (1.3%)	0.119	1.532	3.0 (1.9–4.1)
Other	24 (2.6%)	1913 (3.0%)	NA	NA	5.0 (4.0–6.0)
Tumor size, cm					
≤4	90 (9.6%)	29,863 (46.8%)	<0.001	0.361	3.0 (1.8–4.2)
4–7	187 (20.0%)	17,229 (27.0%)	<0.984	0.997	4.0 (3.1–4.9)
7–10	285 (30.5%)	8400 (13.2%)	0.098	1.276	5.0 (4.0–6.0)
>10	259 (27.8%)	5839 (9.2%)	0.007	1.492	6.0 (4.8–7.2)
Unknown	112 (12.0%)	2476 (3.9%)	NA	NA	4.0 (2.3–5.7)
Fuhrman grade					
Grade 1	14 (1.5%)	5476 (8.6%)	<0.001	0.167	2.0 (0.7–3.3)
Grade 2	79 (8.5%)	23,335 (36.6%)	<0.001	0.170	7.0 (4.8–9.2)
Grade 3	139 (14.9%)	13,089 (20.5%)	<0.001	0.316	9.0 (5.6–12.4)
Grade 4	93 (10.0%)	3276 (5.1%)	<0.001	0.482	7.0 (5.8–8.2)
Unknown	608 (65.2%)	18,631 (29.2%)	NA	NA	4.0 (3.5–4.5)
T stage					
T0	4 (0.4%)	86 (0.1%)	0.279	1.801	NA
T1	159 (17.0%)	40,891 (64.1%)	<0.001	0.273	4.0 (3.1–4.9)
T2	218 (23.4%)	6588 (10.3%)	0.095	0.793	6.0 (4.7–7.3)
T3	283 (30.3%)	11,458 (18.0%)	<0.001	0.597	7.0 (6.0–8.0)
T4	78 (8.4%)	1139 (1.8%)	0.371	0.866	4.0 (3.0–5.0)
Unknown	191 (20.5%)	3645 (5.7%)	NA	NA	3.0 (2.1–3.9)
N stage					
N0	564 (60.5%)	57,432 (90.0%)	<0.001	0.451	6.0 (5.3–6.7)
N1	233 (25.0%)	3481 (5.4%)	0.652	0.945	4.0 (3.3–4.7)
Unknown	136 (14.6%)	2894 (4.5%)	NA	NA	4.0 (2.2–5.8)

Table 1 (continued)

Variable	Multivariate logistic analysis			Exp(B)	Median survival time, months (95% CI)
	With BM (n=933, %)	All RCC (n=63,807, %)	P		
Nephrectomy					
Yes	221 (23.7%)	52,245 (81.9%)	NA	NA	13.0 (9.9–16.1)
No	712 (76.3%)	11,446 (17.9%)	NA	NA	4.0 (3.5–4.5)
Unknown	0 (0.0%)	116 (0.2%)	NA	NA	NA

BM brain metastases, RCC renal cell carcinoma, 95% CI 95% confidence interval, NA no accepted, Other American Indian/AK Native, Asian/Pacific Islander and other races, ccRCC clear cell renal cell carcinoma, pRCC papillary renal cell carcinoma, chRCC chromophobe renal cell carcinoma, sRCC sarcomatoid renal cell carcinoma, CDC collecting duct carcinoma

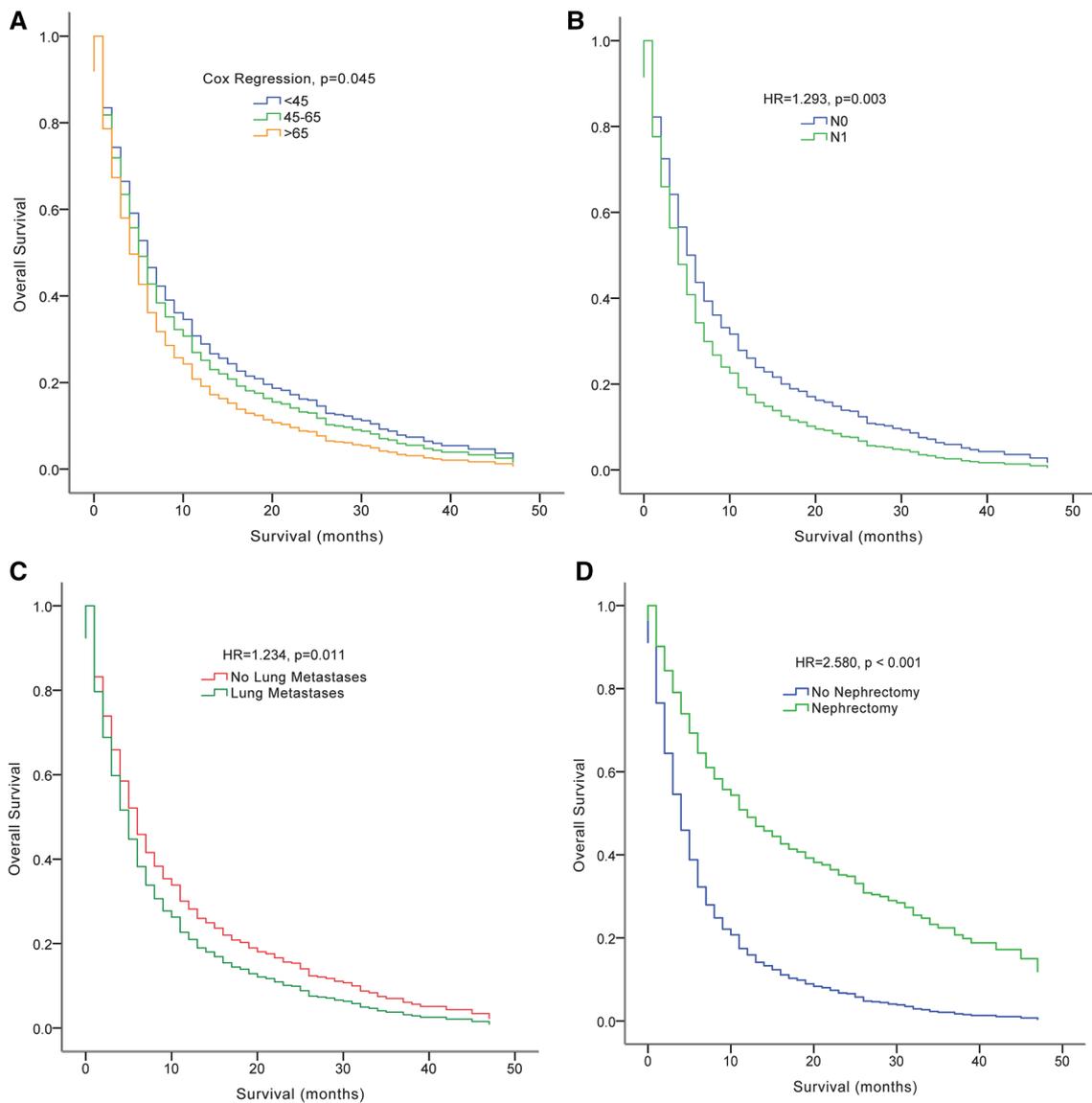


Fig. 1 Survival curves of independent risk factors of renal cell carcinoma with brain metastasis on multivariable Cox regression analysis. **a** Age, the group of < 45 years old had the longest OS and the group of > 65 years old had the shortest OS. **b** N stage, the OS of N0 group

was superior to that of N1 group. **c** Lung metastasis, OS in the group without lung metastasis was superior to that in the group with lung metastasis. **d** Nephrectomy, the OS of patients undergoing surgery was superior to that of patients without surgery

Survival

The median survival time (MST) of RCC patients with BM was 5.0 months [95% confidence interval (95% CI) 4.5–5.5], which was extremely shorter than other distant metastases such as liver and lung (MST 8.0, 95% CI 7.6–8.4) ($P < 0.001$).

Univariate analysis of each variable was performed by the K–M method, and the variable with $P < 0.1$ was selected into the multivariate Cox model to analyze the risk factors of OS. Age ($P < 0.001$), Fuhrman grade ($P < 0.001$), T stage ($P < 0.001$), N stage ($P < 0.001$), bone metastases ($P = 0.003$), liver metastases ($P < 0.001$), lung metastases ($P < 0.001$) and nephrectomy ($P < 0.001$) were significant variables. Race ($P = 0.190$), gender ($P = 0.673$), marital status ($P = 0.879$), insurance status ($P = 0.854$), histologic type ($P = 0.221$) and tumor size ($P = 0.060$) were excluded.

Multivariable Cox regression was performed using the following: LR method. Age ($P = 0.045$), N stage ($P = 0.010$), lung metastases ($P = 0.010$) and nephrectomy

($P < 0.010$) were independent prognostic factors for OS, which were screened out in Step 4 (Fig. 1). Multivariate analysis revealed that: N1 (vs N0, HR 1.293; 95% CI 1.092–1.531; $P = 0.003$), lung metastases (vs without lung metastases, HR 1.234; 95% CI 1.050–1.450; $P = 0.011$) and non-nephrectomy (vs nephrectomy, HR 2.580; 95% CI 2.118–3.143; $P < 0.001$) were significantly associated with an increased all-cause mortality (Table 2).

Nomogram model

The nomogram visualization model was established by R language to predict individualized survival rates at 1 year, 2 years and 3 years for RCC patients with BM. The independent prognostic factors were incorporated into the model as variables, such as age, N stage, lung metastases and nephrectomy. Corresponding to the first column of the model, each variable can calculate a specific score. The four items add up to a total score, which quantify the individual survival rate of patient at 1 year, 2 years and 3 years

Table 2 Multivariate Cox regression analysis of prognostic factors influencing overall survival of patients with brain metastases in renal cell carcinoma

Variable	Univariate analyses		Multivariate analyses	
	Log-rank (χ^2)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Age, years	15.078	0.001		0.045
< 45			Reference	
45–65			1.112 (0.735–1.681)	0.616
> 65			1.332 (0.876–2.027)	0.180
Race	4.763	0.190		
Gender	0.178	0.673		
Marital status	0.258	0.879		
Insurance status	0.316	0.854		
Histologic type	5.725	0.221		
Tumor size, cm	9.037	0.060		
Fuhrman grade	46.783	< 0.001		
T stage	36.890	< 0.001		
N stage	23.707	< 0.001		0.010
N0			Reference	
N1			1.293 (1.092–1.531)	0.003
Unknown			1.175 (0.953–1.448)	0.132
Bone metastases	11.420	0.003		
Liver metastases	22.061	< 0.001		
Lung metastases	29.651	< 0.001		0.010
Yes			1.234 (1.050–1.450)	0.011
No			Reference	
Unknown			1.917 (1.067–3.444)	0.029
Nephrectomy	133.585	< 0.001		< 0.001
Yes	NA	NA	Reference	
No	NA	NA	2.580 (2.118–3.143)	< 0.001

HR hazard ratio, 95% CI 95% confidence interval, *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

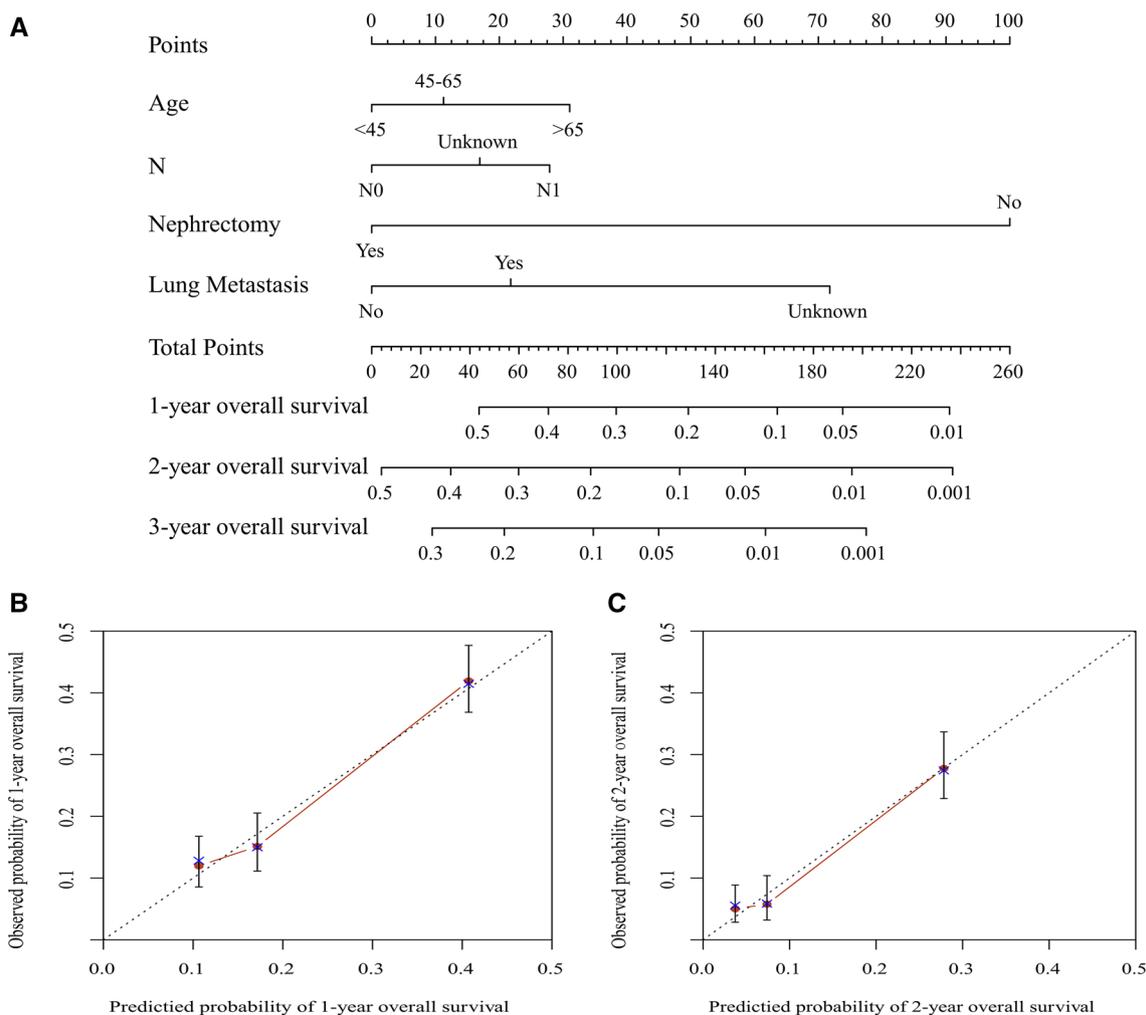


Fig. 2 Prognosis prediction model of renal cell carcinoma with brain metastasis—Nomogram model (a) and calibration curve of survival probability prediction (b). a The score corresponding to "age, N stage, nephrectomy, lung metastasis" are added up to obtain the total point. Corresponding to the scale on total points, the individual sur-

vival rate of the patient at 1-year, 2-year and 3-year can be quantified. b The 1-year and 2-year survival prediction curves of the patients were close to the calibration fitting line (diagonal line), indicating a good predictive ability

according to the model's "total points". The internal verification *c*-index was 0.727 (Fig. 2).

CI 2.8–5.2) of the non-surgery group, and the difference was statistically significant ($P < 0.001$) (Fig. 5).

Propensity score matching analysis

Competing risk model

In addition to the surgical methods, we performed a 1:1 PSM on age, race, gender, marriage status, insurance status, histologic type, tumor size, Fuhrman grade, T stage, N stage, bone metastases, liver metastases, lung metastases and other variables. The matching tolerance was set as 0.1 and 216 cases were successfully matched (Figs. 3, 4).

For the data after PSM, the competitive risk model of CSS was established using R language. The risk of cancer-specific mortality of patients who did not have nephrectomy was higher than that of patients treated with nephrectomy ($P < 0.001$). There was no significant difference between surgical and non-surgical patients in non-cancer mortality (Fig. 5).

On K–M analysis performed on the matched cases, the MST of nephrectomy group was 12.0 months (95% CI 7.9–16.1), which was much higher than the 4.0 months (95%

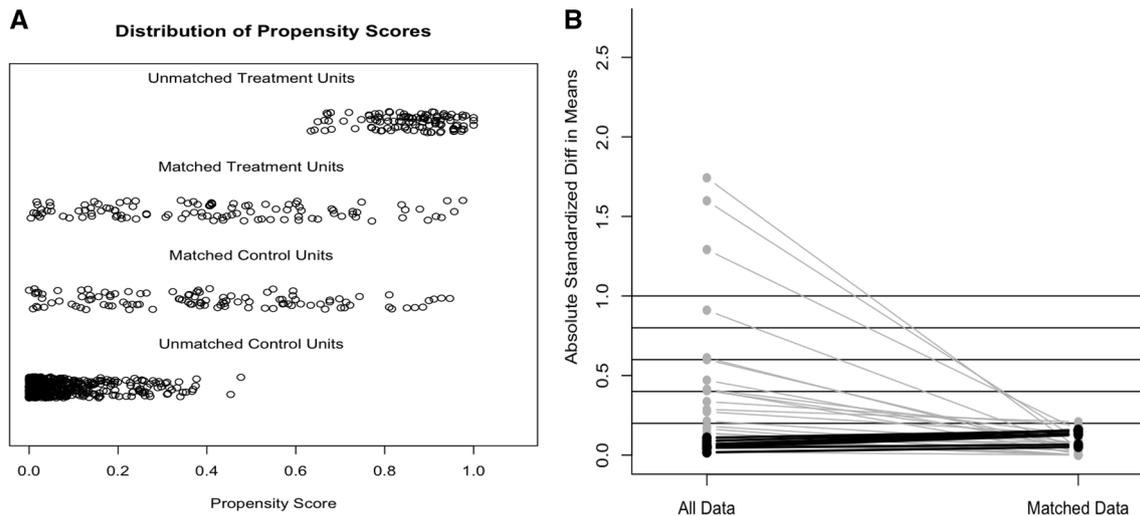


Fig. 3 The distribution map of the propensity score after matching the propensity of brain metastasis of renal cell carcinoma (a) and Line diagram of standardized differences (b). a The individual propensity scores and distribution patterns of the matched individuals

were relatively close, indicating that the matching effect was good. b After matching, most individual standardized differences decreased, indicating that the matching effect is good

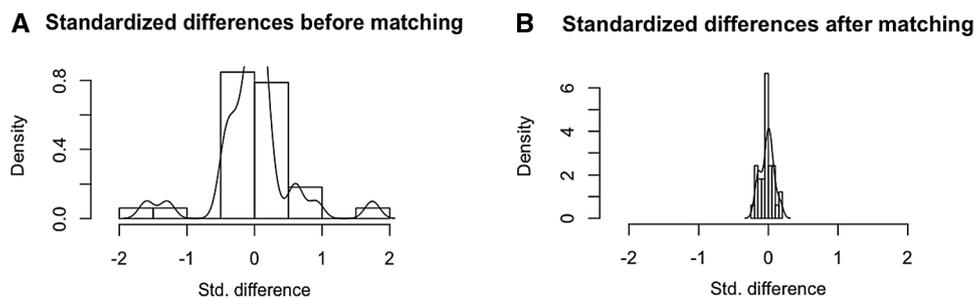


Fig. 4 Histogram of standardized differences distribution before (a) and after (b) matching of brain metastasis of renal cell carcinoma. a The standardized difference of each variable before matching was far away from the 0 axis, indicating that the standardization difference of

the system was large. b The standardized difference of each variable after matching was close to the 0 axis, indicating that the system differences were significantly reduced and the matching was good

Discussion

In our study, we found that: (1) ccRCC patients aged 45–65 years and with tumor diameter > 10 cm have a high risk of BM. Even if the patient has no neurological symptoms, brain imaging screening should be noted during follow-up. (2) It was confirmed that nephrectomy helps to prolong the OS and CSS of patients after matching their general condition and pathological factors with propensity scores. (3) Age, N Stage, lung metastases and nephrectomy were independent prognostic factors for the prognosis of RCC patients with BM. The nomogram visualization model was established based on statistical results for the first time, which attempts to assess the patient’s 1-year, 2-year and 3-year survival rates to aid clinical decision-making.

The incidence of BM in RCC patients is low, but the prognosis is poor. One-third of the patients have asymptomatic metastases [12], and the routine brain imaging for all RCC patients undoubtedly increases social costs. We found that ccRCC patients age 45–65 years with and tumor diameter > 10 cm had a higher risk of BM, while those with tumor diameters ≤ 4 cm, T1 stage, N0 stage and histologic type of pRCC or chRCC had a lower risk of BM. Even if there are no neuropsychiatric symptoms, such as dizziness, headache and altered consciousness, brain imaging should be performed among patients with high risk of metastasis during follow-up.

For metastatic RCC, it is generally believed that surgery only serves as a form of palliative treatment. The survival extension of patients mainly lies in the comprehensive use of

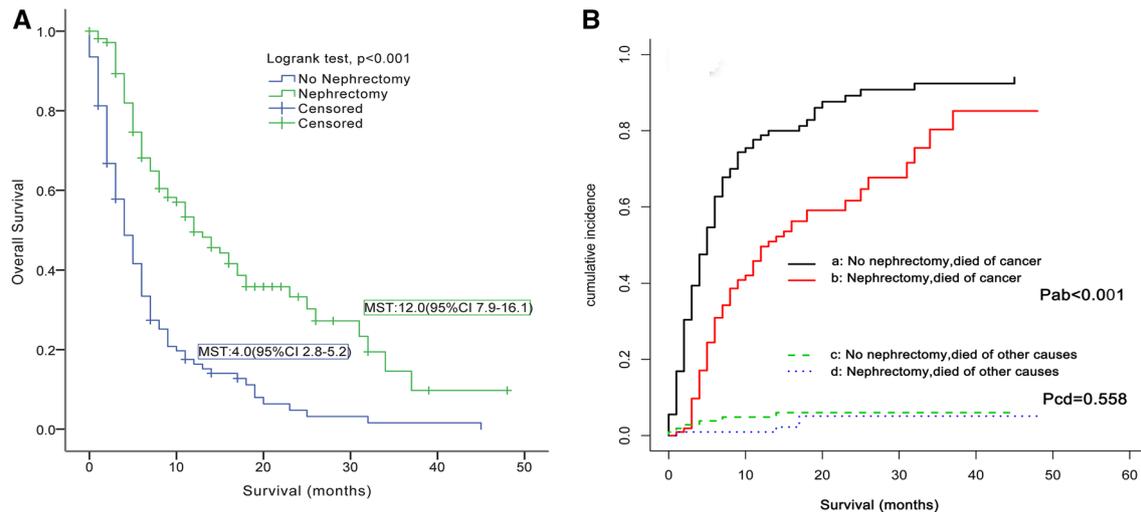


Fig. 5 Kaplan–Meier curves (**a**) of overall survival and Competitive risk curve of cancer-specific survival (**b**) of brain metastasis of renal cell carcinoma after matching. **a** K–M analysis suggested that the OS of the nephrectomy group was significantly better than the non-surgical group. **b** Competitive risk model analysis indicated that the

cancer-specific mortality of the nephrectomy group was significantly lower than that of the non-surgical group. There was no significant difference in the risk of death from non-cancer factors between the two groups

targeted therapies, immunotherapy, chemotherapy and other body therapies. With the emergence of new drugs such as monoclonal antibodies against circulating VEGF, mTOR inhibitors and new immunotherapeutic drugs such as PD-1 and PD-L1, surgical treatment is controversial in the value of M1 stage patients, especially in BM patients with poor prognosis [13]. Proponents believe that aggressive surgical treatment can produce good results in BM patients, including pathological confirmation, rapid reversal of neurological symptoms and no risk of radiation necrosis, which can bring significant survival advantages [12, 14–16]. Opponents argue that surgery would increase complications and in-hospital mortality affecting survival benefits [17–19].

There are few cases of RCC with BM, and limited information based on small, single-institutional patient cohorts is often insufficient for a comprehensive systematic study. Our study covered the statistics of 68,000 newly diagnosed RCC patients in North America during 2010–2014 with representative conclusions. However, it is undeniable that the outcome of survival studies may be affected by selection bias from the retrospective information. For example, patients undergoing surgery may have better behavioral status, and some patients have mild tumor lesions that are isolated and easy to be removed [13, 20, 21]. We performed PSM on general clinical data and tumor pathological features of RCC patients with BM for the first time, which effectively reduced the selection bias error in survival analysis of nephrectomy.

In the study, we found that nephrectomy has significant benefits in the survival of RCC patients with BM. On Cox analysis, the risk of death in patients who did not have

nephrectomy was 2.835 times that of surgical patients. K–M analysis performed on the matched cases revealed that the MST of nephrectomy group was 14.0 months, which was much higher than 5.0 months of the non-surgical group, and the difference was statistically significant. The competitive risk model also confirmed that nephrectomy significantly reduced the cancer-specific mortality of patients.

The nomogram developed in our research was the first visual model to quantify survival rate for the special subgroup of RCC patients with BM [22]. We incorporated independent factors affecting the prognosis into the model to calculate patients' 1-year, 2-year and 3-year survival rates by means of drawing, which is helpful for clinical decision-making. However, the internal verification effect was not as good as expected, and the *c*-index was only 0.727. This may be related to the rapid disease progression and extremely short survival period of BM patients, considering that it is difficult to quantify the survival probability of patients in time. The addition of Karnofsky behavioral functional status score of patients may be helpful to improve the accuracy of the model.

Limitations

Our study successfully revealed the general epidemiological characteristics, survival prognosis and the value of nephrectomy for survival of RCC patients with BM. It is undeniable that the SEER database has its own limitations. For example, we do not know the patient's

comorbidity information, systemic treatment information such as concurrent chemotherapy or targeted therapy [21] and information on the number or size of brain metastases, as well as the Karnofsky behavioral functional status scores. The lack of information may play a role affecting the survival of patients [23], so there were still some errors in the conclusion obtained. However, with the accurate epidemiology, tumor pathology information and surgical data acquired from a large amount of data, combined with the propensity score matching, the research conclusions are still of good representativeness and clinical research guidance value.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. We obtained the authorization to access the SEER database, with the number 14260-Nov 2016.

Informed consent The SEER database does not reveal patient privacy, so patient informed consent is not required.

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